SUMMARIZED BOOK.

MICROBIOLOGY

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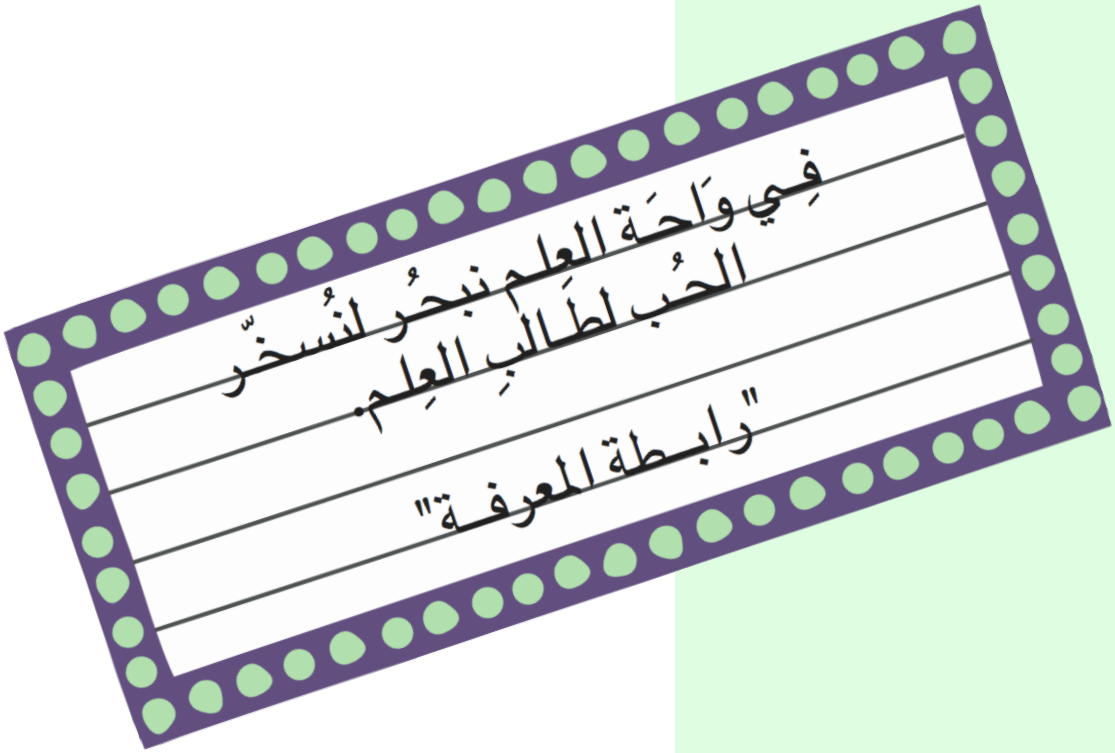

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CHAPTER 1

Introduction to Microbiology

OVERVIEW

Microorganisms can be found in every ecosystem and in close association with every type of multicellular organism. Most infection disease is initiated by colonization (the establishment of proliferating microorganisms on the skin or mucous membranes). Microbial colonization my result in:

1) Elimination of the microorganisms without affecting the host.

2) Infection in which the organisms multiply and cause the host to react by making an immune or other type of response or a transient or prolonged carrier state.

Infectious disease occurs when the organism causes tissue damage and impairment of body function.

PROKARYOTIC PATHOGENS

All prokaryotic organisms are classified as bacteria. Prokaryotic organisms are divided into two major groups: the euba-cteria, which include all bacteria of medical importance, and the archae-bacteria, a collection of evolutionarily distinct organisms. Comparison of prokaryotic and eukaryotic cells.

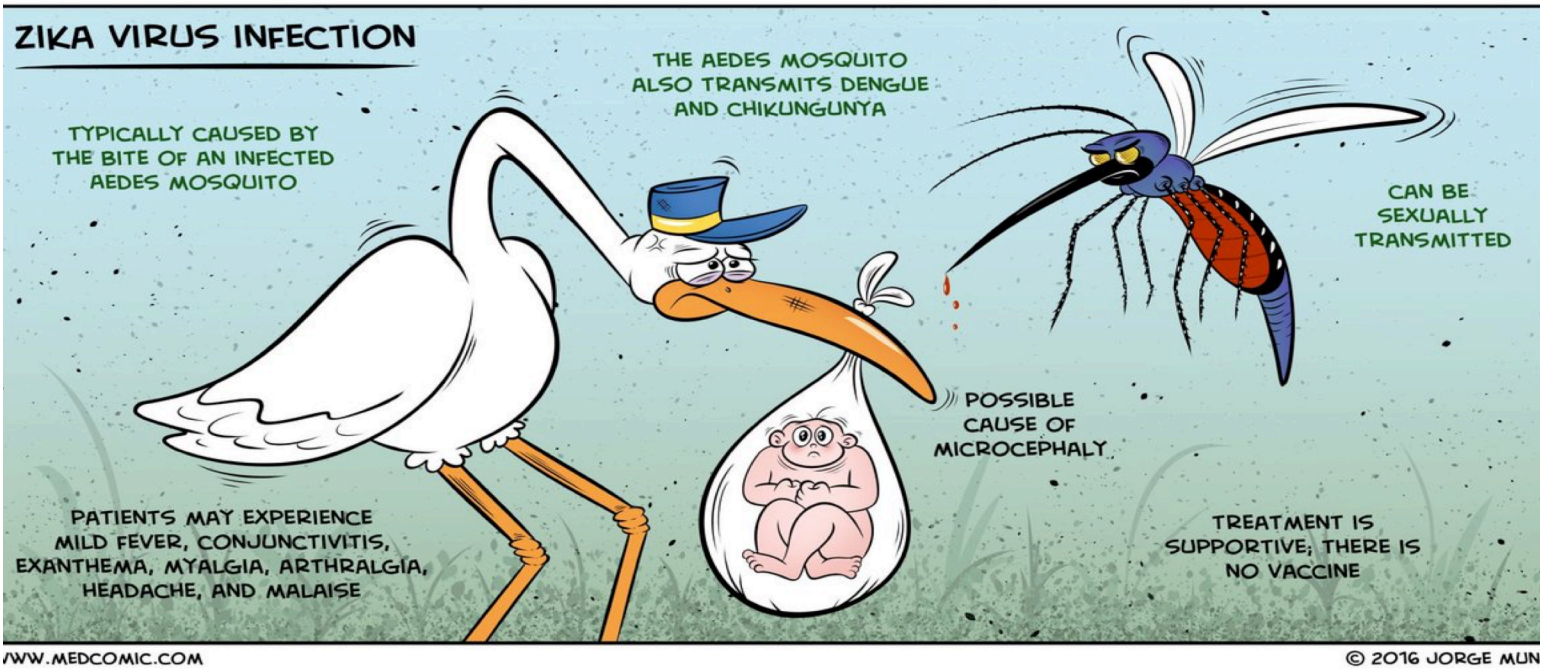
CHARACTERISTIC	PROKARYOTIC CELLS	EUKARYOTIC CELLS
Chromosome	Usually single ,circular	Multiple
Nucleus	No nuclear envelope	Nucleoli present
Membrane bound organelles	No present	present
Cell wall	Usually present, contain peptidoglycan	Present in plant cell , no peptidoglycan
Plasma membrane	No carbohydrates , most lack sterol	Sterol and carbohydrates present
Ribosome	70S	80S
Average size	0.2-2mm in diameter	10-100mm in diameter

A. Typical bacteria

Most bacteria have shapes that can be described as a rod, sphere , or corkscrew . The cell wall determines whether the bacterium is classified as gram positive or gram negative. External to the cell wall may be flagella, pili, and a capsule. Bacterial cells divide by binary fission. Many bacteria exchange genetic information carried on plasmids (small , specialized genetic elements capable of self-replication).

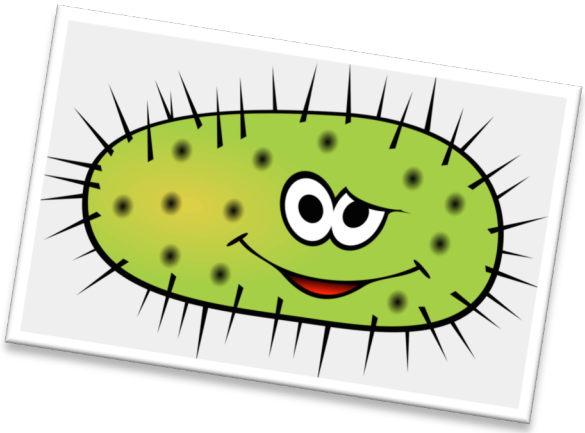
B. Atypical

Atypical bacteria include groups of organisms sush as Rickettsia that , although prokaryotic, lack significant characteristic structural components or metabolic capabilities that sparate them from the larger group of typical bacteria.



CHAPTER 2

Normal flora



Normal flora: it's a microorganism that also known as commensals (means: organisms that dine together). Our internal organs and system are sterile *(free from living microorganism)* including the spleen, pancreas, liver, bladder, CNS, and blood. A healthy newborn enter the world in essentially sterile condition, but, after birth, they rapidly acquires normal flora from food, environment, and other humans.

THE HUMEN MICROBIOME:

The human microbiome is the total number and diversity of microbes that found in and on the human body. In the past, the gold standard to identify the normal flora and bacterial pathogens was by cultivating organism from tissues and clinical samples. Nowadays, they're an application of culture-independent molecular detection methods based on DNA sequencing indicates that the human body contains a greater bacterial diversity than previously recognized. The molecular detection requires neither prior knowledge of an organism not the ability to culture it. Thus, molecular methods are able to detect fastidious and nonculturable species. It is difficult to define the human microbiome because microbial species vary from individual to another due to physiologic differences, diet, age, and geographic habitat. Even though it's difficult, it's useful to know the dominant types and distribution of resident flora, because with knowledge we well understand the possible infections that result from injury to particular body site.

Distribution of normal flora in the body :

The most common sites for normal flora in the body is the sites that communicate with outside world, namely**, the skin, eye, URT, GIT, urogenital tracts and mouth.**

A. skin

Skin can acquire any bacteria from the immediate environment. But, they either die or remove by washing. Nevertheless, the skin supports a permanent bacterial population (resident flora). They rest in multiple layers of the skin and regenerate even after vigorous scrubbing.

1) Estimate of the skin microbiome using classical culture techniques: aerobeic organism rest in the outer layer of the skin such as S.epidermidis and other coagulase –ve staphylococci, account for some 90% of the skin aerobes. Anaerobic ones rest in deeper skin layers, hair follicles, and sweat gland, e.g. propionibacterium acnes. Skin flora is harmless and can lead to serious blood infections if it penetrates through the skin. 2) Estimate of the skin microbiome using molecular sequencing techniques: the estimate of the number of species that found on the skin bacteria has been radically changed by the use of 16S ribosomal RNA gene sequence. In the past, identification had depended on microbiological

culture, and how many varieties of bacteria didn't grow and didn't detect. From culture based research s.epidermidis and S.aureus though to be the dominant. But, after DAN analysis research finds that they only make up 5% of skin bacteria.

B. Eye Tears contain antimicrobial enzyme lysozyme; help limit the bacteria population of the conjunctiva. The conjunctiva of the eye is colonized primarily, by S.epidermidis , S.aureus , aerobic corynebacteria and S.pneumoniae. Other organism that found in the skin also present but at low frequency.

C. Mouth and Nose: They contain both aerobic and anaerobic organism. The most common ones is aerobic corynebaterium ,S.aureus and S.epidermidis. In addition, the teeth and gingival tissue are colonized by there own particular species such as S.mutans. (**Note:** after dental surgery the S.mutans can enter the bloodstream and colonized in the heart valve leading to potentially fatal infective endocarditis). In the nasopharynx S.pneumoniae can cause acute bacterial pneumonia, which affect the elderly and those who have low resistance the most. (**Note:** pneumonia is preceded by an upper or middle respiratory viral infection, predisposes the individual to S.pneumoniae infection of the pulmonary parenchyma).

D. Intestinal tract

Adult stomach has low density of microorganism due to gastric enzyme and gastric acidity .The microorganism increase along the alimentary canal. About 20% of the fecal mass has a different species of bacteria more than 99% are anaerobic. Bacteroides species found in high percentage in the large intestine. While the E.coli facultatively anaerobic organism found less than 0.1% . However, the endogenous E.coli consider being the major cause of urinary tract infection.

E. Urogenital tract

Adult vagina has low PH due the percent of the Lactobacillus specie, if the Lactobacillus decreased the PH arise and it well lead to overgrowth of pathogens. Best example for that is the overgrowth of yeast like fungi "Candida albicans" which itself a minor member of the normal flora of the vagina, mouth, and small intestine. In addition, Urine in the kidney and bladder may become contaminated in the lower urethra by the same organism that inhabits the outer layer of the skin and perineum.

Beneficial Function of Normal Flora

1/ The sheer number of harmless bacteria in Lower bowl and mouth make it unlikely that, in a healthy person, an invading pathogen could compete for nutrition and receptor site.
2/ Stimulates the development of the immune system in newborns
3/ Produce antimicrobial substance form some bacteria
4/ Provide important nutrition like vitamin **k** and aid in absorption and digestion of nutrition

Harmful Effects of Normal Flora

1/ Displaced from their normal site in the body to an abnormal site. An example S. epidermidis, enter the bloodstream and colonized in the heart valves, resulting in endocarditis.
2/ Pathogens gain a competitive advantage due to diminished of the harmless competitors.
3/ Harmless, commonly ingested food substances are converted into carcinogenic derivatives by bacteria in the colon.
4/ Normal flora can overgrow and become pathogenic when the immunity is impaired.

CHAPTER 3

Pathogenicity of Microorganisms

OVERVIEW

A pathogenic microorganism is defined as one that is capable of caus-ing disease .
An organism may invade an individual without causing infectious disease when the host's defense mechanisms are successful. Some infections result in latent state, meaning that the organism is dormant but may reacti-vated with the recurrence of symptoms .Moreover, some pathogens cause disease only under certain conditions .

BACTERIAL PATHOGENESIS.

Although the mechanism of infectious process may vary among bacteria, the methods by which bacteria cause disease can, in general, be divided into several stages .The number of organisms required to cause disease varies greatly among pathogenic bacteria .The infectious dose of a bacterium depend primerialy on virulence factors .

A. Virulance factors

Virulence factors are those characteristics of a bacterium that enhance its pathogenicity ,that enable a micro organism to establish itself and replicate on or within a specific host . Some of the more important steps in the infectious process are reviewed below.

1. Entry into the host: The first step of the infectious process is the entry of the microorganism into the host by one of several ports: via the respiratory, GI, or urogenital tract or through skin that has been cut, punctured, or burned. Once entry is achieved pathogen must overcome diverse host defenses before it can establish itself.

2. Adherence to host cells: Some bacteria use pili to adhere to the surface of

host cells. Adherence enhances virulence by preventing the bacteria from being carried away by mucus or washed from organs with significant fluid flow, such as the urinary and the GI tracts. Adherence also allows each attached bacterial cell to form a microcolony.

3. Invasiveness: Invasive bacteria are those that can enter host cells or penetrate mucosal surfaces, spreading from the initial site of infection. Invasiveness is facilitated by several bacterial enzymes, the most notable of which are collagenase and hyaluronidase .

4. Iron sequestering:

Iron is an essential nutrient for most bacteria . To obtain the iron required for growth bacteria produce iron-bind-ing compounds, called siderophores .

5. Virulence factors that inhibit phagocytosis:

The most important antiphagocytic structure is the capsule external to the cell wall .

6. Bacterial toxins.

Some bacteria cause disease by producing toxic substances, of which there are two general types: exotoxins and endotoxin. Exotoxins, which are proteins, are secreted by both gram-positive and gram-negative bacteria.

a. Exotoxins :These include some of the most poisonous substances known.

Exotoxin proteins generally have two polypeptide components .One is responsible for binding the protein to the host cell and one is responsible for the toxic effect.

b. Endotoxins :

These are heat-staple ,LPS components of the outer membranes of gram-negative (but not gram-positive) bacteria . they are released into the host's circulation following bacterial cell lysis .

B. Host mediated pathogenesis.

The pathogenesis of many bacterial infections is caused by the host response rather than by bacterial factors. The tissue damage in these infections is caused by various cytokines released from the lymphocytes, macrophages, and polymorphonuclear leukocytes at the site of infection or in the blood stream.

C. Antigenic variation

A successful pathogen must evade the host’s immune system that recognizes bacterial surface antigens .This is accomplished by several mechanisms .One mechanism , called phase variation , is genetically reversible ability of certain bacteria to turn off and turn on the expression of genes coding for surface antigens . called antigenic variation , involves A second mechanism the modification of the gene for an expressed surface antigen by genetic recombination with one of many variable unexpressed DNA sequences .

D. Which is the pathogen ?

Isolating a particular microorganism from infected tissue,does not conclusively demonstrate that it coused the lesion.

E.Infections in human populations

Bacterial diseases may be communicable from person to person or noncommunicable.

VIRAL PATHOGENESIS

Viruses can replicate only inside living cells.

A.viral pathogenesis at the cellular level

Cells show a variety of different responses to viral infection , depending on the cell type and virus .

1. Cell death:

A cell can be directly killed by the virus . In most cases , this is due to the inhibition of synthesis of cellular DNA,RNA, and protein .

2. Transformation:

Some virus transform normal cells into malignant cells .

3. Cell fusion: Infection of cells with certain viruses causes the cells to fuse , producing gaint , multinucleate cells . The ability of infected cells to fuse is apparently due to virus-in duced changes in the structure of the cell membrane .

4. Cytopathic effect:

Cytopathic effect (CPE) is a catch-all term that revers to any visible change in appearance of an infected cell . Some viruses can be roughly identified by the time of onest and pattern of CPE in cell culture as well as by the types of cells in which these viruses cause CPE.

B . Initial infections :

Following initial multiplication at the primary site of entry .

The viral infection may remain localized or become disseminated .

The infection may be asymptomatic (unapparent) .

1. Routes of entry and dissemination to secondary sites :

Common routes by which viruses enter the body are essentially the same as for bacterial infections.

In each cases , some viruses remain local-lized and cause disease that is largely restricted to the primary site of infection .

2 . Typical secondary sites of localization :

Secondary sites of infection determine the nature of the delayed symptoms and , usually , the major characteristics associated with the resulting disease .

3 . virus shedding and mode of transmission:

The mode of transmission of a viral disease is largely determined by the tissues that produce progeny virus and the fluids into which they are released .

4 . Factors involved in termination of acute infection :

in a typical uncomplicated , acute infection , virus is totally eliminated from the host in 2 to 3 weeks . this is outcome is primarily a function of the host's immune system , with involvement of both cell-mediated and humoral responses .

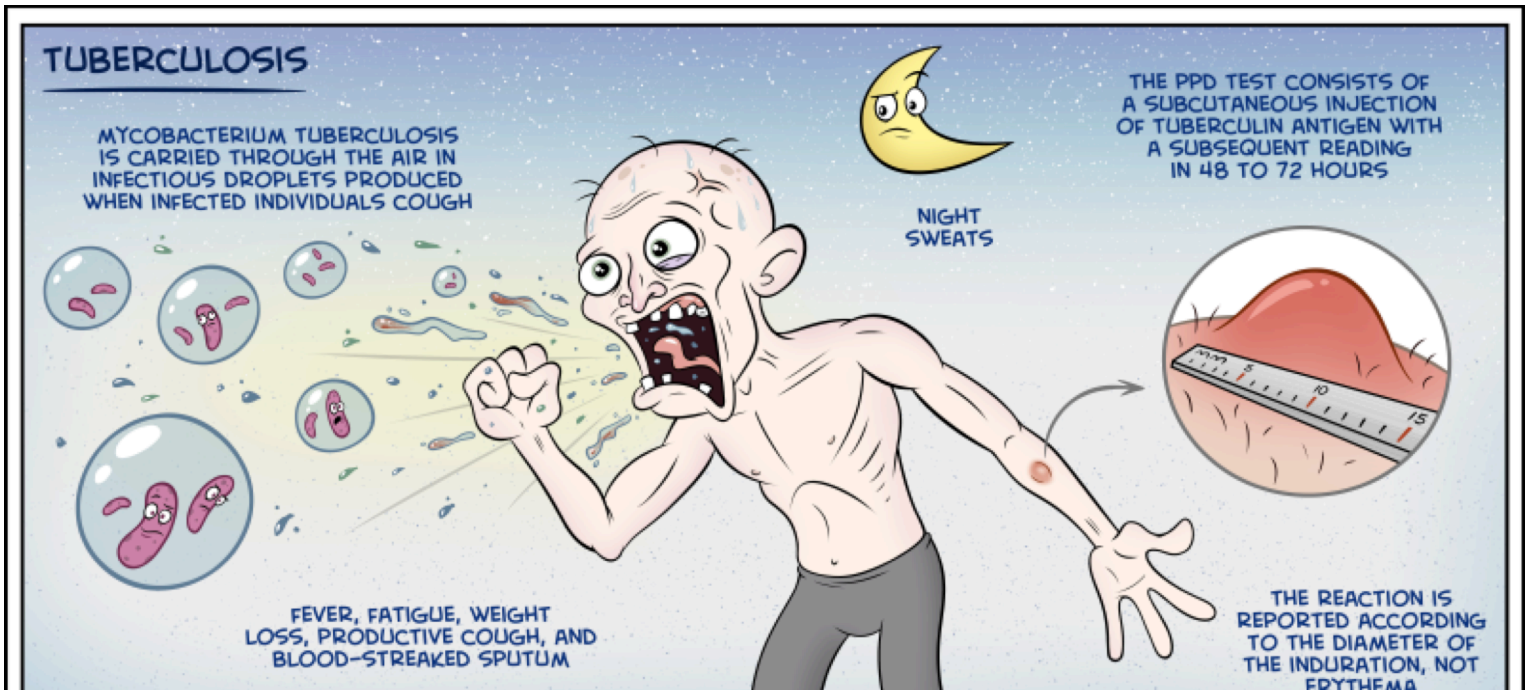
a . Cell mediated responses:

The earliest immune system response to virus infection is a generalized inflammatory response , accompanied by nonspecific killing of infected cells by natural killer cells .

This latter activity , enhanced by inter-feron and other cytokines , begins well before the virus-specific immune response .

b . Humoral response :

Although circulating antibodies may be directed against any virus protein, those that are of greatest significance in controlling an infection react specifically with epitopes on the surface of the virion and result in inactivation of the virus's infectivity .The process is called neutralization.



CHAPTER 4

Diagnostic Microbiology

I. OVERVIEW

Identifying the organism causing an infectious process is usually essen tial for effective antimicrobial and supportive therapy .Initial treatment may be empiric, based on the microbiologic epidemiology of the Infection and the patient's symptoms. However, definitive microbiologic diagnosis of an infectious disease usually involves one or more of the following five basic laboratory techniques, which guide the physician along a narrowing path of possible causative organisms: 1) direct micro scopic visualization of the organism, 2) cultivation and identification of the organism, 3) detection of microbial antigens, 4) detection of microbial DNA or RNA, and 5) detection of an inflammatory or host immune response to the microorganism .

PATIENT HISTORY AND PHYSICAL EXAMINATION .

A clinical history is the most important part of patient evaluation. A history of travel to developing countries may implicate exotic organisms. Patient occupations may sug-gest exposure to certain pathogens , such as brucellosis in a butcher or anthrax in farmers .

Even the age of the patient can sometimes guide the clinician in predicting the identity of pathogens. The etiology implied by the patient's age may thus guide initial therapy. A physical examination often provides confirmatory clues to the presence and extent (localized or disseminated) of disease.

DIRECT VISUALIZATION OF THE ORGANISM

In many infectious diseases , pathogenic organisms can often be directly visualized by microscopic examination of patient specimens be examined do not need to be alive or able to multiply The organisms to

A. Gram stain

Because unstained bacteria are difficult to detect with the light microscope, most patient material is stained prior to microscopic evaluation.

The most common and useful staining procedure is the Gram stain, which separates bacteria into two classifications according to their cell wall composition.

1-Gram stain applications

The gram stain is important therapeutically because gram positive bacteria differ in their susceptibility to various antibiotics, and the gram stain may , therefore , be used to guide initial therapy until the microorganism can be definitively identified .

Gram stains of specimens submitted for culture are often invaluable aids in the interpretation of culture results.

2- Gram stain limitations.

The number of microorganisms required is relatively high. 104 than Visualization with the Gram stain requires greater mL /organisms.The pellet is then examined after staining

B. Fast stain

Acid most bacteria that have been stained with carbol fuchsin can be decolorized by washing with acidic alcohol. However, certain acid-fast bacteria retain the carbolfuchsin stain after being washed with an acidic solution C.India ink preparation This is one of the simplest microscopic methods. It is useful in detecting Cryptococcus neoformans in CSF.

D. Potassium hydroxide preparation .

Treatment with potassium hydroxide (KOH) dissolves host cells and bacteria, sparing fungi .

GROWING BACTERIA IN CULTURE

Culturing is routine for most bacterial and fungal infections but is rarely used to identify helminths or protozoa. Culturing of many pathogens is straightforward, for example, streaking a throat swab onto a blood agar plate in search of group A β-hemolytic streptococcus. However, certain pathogens are very slow growing or are cultured only with difficulty .

A. Specimen collection

Many organisms are fragile and must be transported to the laboratory with minimal delay . For example, gonococci and pneumococci are very sensitive to heating and drying. Samples must be cultured promptly, or, if this is not possible, transport media must be used to extend the viability of the organism to be cultured.

B. Growth requirements

All clinically important bacteria are heterotrophs (that is, they require organic carbon for growth). Heterotrophs may have complex or simple requirements for organic molecules .

C. Oxygen requirements

Bacteria can be categorized according to their growth responses in the presence and absence of oxygen. Strict aerobes cannot survive in the absence of oxygen and produce energy only by oxidative phosphorylation.rgy by fermentation Strict anaerobes generate ene

. or by anaerobic respiration and are killed in the presence of oxygen

Media .D

Two general strategies are used to isolate pathogenic bacteria depending on the nature of the clinical sample .The first method uses enriched media to promote the nonselective growth of any bacteria that may be present . The second approach employs selective media , that only allow growth of specific bacterial species from specimens that normally contain large numbers of bacteria .

Enriched media 1.

Media fortified with blood, yeast extracts, or brain or heart infusions are useful in growing fastidious organisms . Enriched media are useful for culturing normally sterile body fluids, such as blood and CSF, in which the finding of and organisms provides reasonable evidence for infection by that organism .

Selective media 2.

The most commonly used selective medium is MacConkey agar ،which supports the growth of most gram negative rods, especially the Enterobacteriaceae, but inhibits growth of gram positive organisms and some fastidious gram negative bacteria, such as Haemophilus and Neisseria species .

Growth on blood agar and chocolate agar but not MacConkey agar suggests a gram-positive isolate or a fastidious gram-negative species.

.IDENTIFICATION OF BACTERIA

The most widely used identification scheme involves determining the morphologic and metabolic properties of the unknown bacterium and comparing these with properties of known microorganisms .

enzyme tests SingleA.

Different bacteria produce varying spectra of enzymes

Tests that measure single bacterial enzymes are simple, rapid, and generally easy to interpret .

They can be performed on organisms already grown in culture and often provide presumptive identification.

1. Catalase test:

The enzyme catalase catalyzes the degradation of hydrogen peroxide to water and molecular oxygen.

Catalase positive organisms rapidly produce bubbles when exposed to a solution containing hydrogen peroxide.

Catalase-positive organisms rapidly produce bubbles when exposed to a solution containing hydrogen peroxide. For example, staphylococci are catalase positive, whereas streptococci and enterococci are catalase negative

2. Oxidase test

The enzyme cytochrome c oxidase is part of electron transport and nitrate metabolism in some bacteria .

The enzyme can accept electrons from artificial substrates .

2. Urease

The enzyme urease hydrolyzes urea to ammonia and carbon dioxide .

3. Coagulase test

Coagulase is an enzyme that causes a clot to form when bacteria are incubated with plasma .

The test is used to differentiate Staphylococcus aureus from coagulase negative staphylococci .

B. Automated systems

Microbiology laboratories are increasingly using automated methods to identify bacterial pathogens .

An inoculum derivedfrom cultured samples is automatically transferred into the card, and a photometer intermittently measures color changes in the card that result from the metabolic activity of the organism.

C. Tests based on the presence of metabolic pathways

These tests measure the presence of metabolic pathways in a bacterial isolate, rather than a single enzyme .

Commonly used assaysinclude those for oxidation and fermentation of different carbohydrates, the ability to degrade amino acids, and use of specific substrates .

The test substrates in the microtubesare inoculated with the bacterial isolate to be identified, and, after 5 hours incubation, the metabolic profile of the organism is constructed from color changes in the microtubes .

VI. IMMUNOLOGIC DETECTION OF MICROORGANISMS

In the diagnosis of infectious diseases, immunologic methods take

advantage of the specificity of antigen antibody binding . Immunologic methods are useful when the infecting microorganism is difficult or impossible to isolate or when a previous infection .

A. Detection of microbial antigen with known antiserum

These methods of identification are often rapid and show favorable sensitivity and specificity .

1. Quellung reaction

Some bacteria having capsules can be identified directly in clinical specimens by a reaction that occurs when the organisms are treated with serum containing specific anti-bodies.

The Quellung reaction makes the capsule more refractile and thus more visible, but the capsule does not actually swell.

2. Slide agglutination test

Some microorganisms, such as Salmonella and Shigella species, can be identified by agglutination (clumping) of a suspension of bacterial cells on a microscopic slide.

B. Identification of serum antibodies

Detection in a patient's serum of antibodies that are directed against microbial antigens provides evidence for a current or past infection with a specific pathogen. A discussion of the general interpretation of antibody responses includes the following rules: 1) antibody may not be detectable early in an infection, 2) the presence of antibodies in a patient's serum cannot differentiate between a present and a prior infection, and 3) a significant rise in antibody titer over a 10 to14 day period does distinguish between a present or prior infection.

1. Complement fixation

One older but still useful method for detecting serum antibody directed against a specific pathogen employs the ability of antibody to bind complement.

A patient's serum is first incubated with antigen specific for the suspected infectious agent, followed by the addition of complement.

2. Direct agglutination

Direct bacterial agglutination testing is sometimes ordered when a suspected pathogen is difficult or dangerous to culture in the laboratory.

This test measures the ability of a patient's serum antibody to directly agglutinate specific killed (yet intact) microorganisms .

3.Direct hemagglutination

Antibodies directed against RBCs can arise during the course of various infections.

When uncoated native) animal or human RBCs are used in agglutination reactions with serum from a patient infected with such an organism antibodies to RBC antigens can be detected. The patient's antibodies cause the RBCs to clump. Other tests used to identify serum antigens or antibodies.

1.Latex agglutination test

Latex and other particles can be readily coated with either antibody or antigen . Addition of antigen to antibody-coated latex beads causes agglutination that can be visually observed

2.Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assay (ELISA) is a diagnostic technique in which antibody specific for an antigen of interest is bound to the walls of a plastic microtiter well .

Patient serum is then incubated in the wells, and any antigen in the serum is bound by antibody on the well walls

3.Fluorescent-antibody tests

Organisms in clinical samples can be detected directly by specific antibodies coupled to a fluorescent compound such as fluorescein. In the direct immunofluorescence antibody technique, a sample of concentrated body fluid , tissue scraping , or cells in tissue culture is incubated with a fluorescein-labeled antibody directed against a specific pathogen .

VII. NUCLEIC ACID –BASED TESTS

The most widely used methods for detecting microbial DNA fall into three categories: 1) direct hybridization (nonamplified assay),

2) amplifycation methods using the polymerase chain reaction (PCR)1 or one its variations, and 3) DNA microarrays .

A. Direct detection of pathogens without target amplification

This highly specific method of pathogen detection involves identify cation of the DNA of the pathogen in a patient sample or, more commonly, organisms isolated in culture. .

B. Nucleic acid amplification for diagnosis

Nucleic acid amplification overcomes the principal limitation of direct detection with nucleic acid probes by selectively amplifying specific DNA targets present in low concentrations .

The bacterial 16S rRNA gene has emerged as the most useful marker for microbial detection. Ribosomal DNA genes contain highly conserved areas (that are used as targets for primers) separated by internal transcribed sequences containing variable, species-specific regions.

1.Conventional polymerase chain reaction

In this method, DNA polymerase repetitively amplifies targeted portions of DNA. Each cycle of amplification doubles the amount of DNA in the sample, leading to an exponential increase in DNA with repeated cycles of amplification. The amplified DNA sequence can then be analyzed by gel electrophoresis, Southern blotting, or direct sequence determination.

2.Real-time polymerase chain reaction

This variant of PCR combines nucleic acid amplification and fluorescent detection of the amplified product in the same closed automated system.

3.Advantages of polymerase chain reaction

Methods employing nucleic acid amplification techniques have a major advantage over direct detection with nucleic acid probes because amplification methods allow specific DNA or RNA target sequences of the pathogen to be amplified millions of times without having to culture the microorganism itself for extended periods

4.Applications

Nucleic acid amplification techniques are generally quick, easy, and accurate. A major use of these techniques is for the detection of organisms that cannot be grown in vitro or for which current culture techniques are insensitive.

5.Limitations

PCR amplification is limited by the occurrence of spurious false positives due to cross contamination with other microorganisms' nucleic acid. PCR tests are often costly and require skilled personnel.

C. DNA microarrays

Although microarrays are now routinely used to measure gene expression, the technique is an emerging technology in the diagnostic microbiology laboratory.

Microarrays have the unprecedented potential to simultaneously detect and identify many pathogens from the same specimen.

.Diagnostic use of microarrays 1

A DNA microarray consists of microscopic spots of immobilized DNA oligonucleotides, each containing specific DNA sequences, known as probes .

VIII. SUSCEPTIBILITY TESTING

After a pathogen is cultured, its sensitivity to specific antibiotics serves as a guide in choosing antimicrobial therapy Some pathogens, such as Streptococcus pyogenes and N. meningitidis, usually have predictable sensitivity patterns to certain antibiotics.

CHAPTER 5
Vaccines and Antimicrobial Agents

OVERVIEW

A vaccine is a biological preparation that enhances immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to produce specific anti- bodies or a cellular immune response that destroys or neutralizes the microorganism or its toxins. Protection of individuals from disease by vaccination can take two forms: passive or active immunization

A. Disk-diffusion method

The classic qualitative method to test susceptibility to antibiotics has been the KirbyBauer diskdiffusion method, in which disks with exact amounts of different antimicrobial agents are placed on culture dishes inoculated with the microorganism to be tested.

B. Minimal inhibitory concentration

Quantitative testing uses a dilution technique in which tubes containing serialdilutions of an antibiotic are inoculated with the organism whose sensitivity to that antibiotic is to be tested. The tubes are incubated and later observed to determine the minimal inhibitory concentration of the antibiotic necessary to prevent bacterial growth.

C. Bacteriostatic versus bactericidal drugs

As noted above, antimicrobial drugs may be bacteriostatic or bactericidal.

Bacteriostatic drugs arrest the growth and replication of bacteria at serum levels achievable in the patient, thereby limiting the spread of infection while the body’s immune system attacks, immobilizes, and eliminates the pathogens.

If the drug is removed before the immune system has scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection.

II. PASSIVE IMMUNIZATION	III. ACTIVE IMMUNIZATION
- Is achieved by injecting a recipient with preformed immunoglobulins (Igs) obtained from human. **- Provides immediate protection to individuals who have been exposed to an infectious and who lack active immunity to that pathogen.** **- Because it does not activate the immune system, it generates no memory response. .** **- Dissipates after a few weeks to months as the Igs are cleared from the recipient's serum.** **- Two basic formulations of prepared Igs have been developed: one from the serum of pooled human donors and one from serum obtained from hyperimmune donors.**	-Is achieved by injection of viable or nonviable pathogens, or purified pathogen product, prompting the immune system to respond as if the body were being attacked by intact infections. - May require several days to months to become effective. - Active immunization leads to prolonged immunity and is generally preferred over the short-term immunity provided by passive immunization with preformed Igs.

A. Formulations for active immunization

Vaccines are: 1) live pathogens. 2) Killed microorganisms. 3) Microbial extracts. 4) Vaccine conjugates. 5) Inactivated toxins (toxoids). Both bacterial and viral pathogens are targeted by these diverse means.

1. Live pathogens: When live pathogens are used, they are attenuated (weakened) to preclude clinical consequences of infection. Attenuated microbes reproduce in the recipient, typically leading to a more robust and long-lasting immune response than can be obtained through vaccination with killed organisms. However, with live, attenuated vaccines, there is a possibility that the attenuated vaccine strain will revert to an active pathogen after administration to the patient.

2. Killed microorganisms: Killed vaccines have the advantage over attenuated microorganisms in that they pose no risk of vaccine-associated infection. As noted above, killed organisms often provide a weak or short-lived immune response.

3. Microbial extracts: Instead of using whole organisms, vaccines can be composed of antigen molecules (often those located on the surface of the microorganism) extracted from the pathogen or prepared by recombinant DNA techniques. The efficacy of these vaccines varies. In some instances, the vaccine antigen is present on all strains of the organism, and the vaccine, thus, protects against infection by all strains.

4. Vaccine conjugates: Vaccines can produce humoral immunity through B cell proliferation leading to antibody production, which may or may not involve helper T cells. For example, pneumococcal polysaccharide and the polysaccharide of Hib induce B-cell type- specific protective antibody without involvement of helper T cells.

5. Toxoids: These are derivatives of bacterial exotoxins produced by chemically altering the natural toxin or by engineering bacteria to produce harmless variants of the toxin. Vaccines containing toxoid are used when the pathogenicity of the organism is a result of the secreted toxin. Depending on the specific vaccine, administration is generally via intramuscular or subcutaneous routes.

B. Types of immune response to vaccines

Vaccines containing killed pathogens or antigenic components of pathogens do not enter host cells, thereby eliciting a primary B cell–mediated humoral response. These antibodies are ineffective in attacking intracellular organisms. By contrast, attenuated live vaccines do penetrate cells. This results in the production of intracellular antigens that are displayed on the surface of the infected cell, prompting a cytotoxic T-cell response, which is effective in eliminating intracellular pathogens.

C. Effect of age on efficacy of immunization

1. Passive immunity from mother: Newborns receive serum IgG antibodies from their mothers, which gives them temporary protection .In addition, maternal milk also contains secretory antibodies provide protection against (GIT) and respiratory tract infections.

2. Active immunization: The infant's antibody develops slowly during the first year of life. Although the immune system is not fully developed, it is desirable to begin immunization at age 2 months because diseases are common in this age group and can be particularly severe.

D. Adverse reactions to active vaccination

Adverse consequences of vaccinations range from mild to severe and even life threatening. Symptoms vary among individuals and with the nature of the vaccination. Among the most common and mildest consequences of immunization are tenderness and swelling at the site of injection and a mild fever.

BACTERIAL VACCINES

A. Less common bacterial pathogens:

1. Anthrax (Bacillus anthracis): Anthrax vaccine consists of a non- infectious sterile filtrate from the culture of an attenuated strain of B. anthracis that contains no dead bacteria. The filtrate is adsorbed to an adjuvant, aluminum hydroxide.
2. Cholera (Vibrio cholerae): The vaccine contains killed bacteria and is given to individuals traveling to areas with increased risk of acquiring cholera.
3. Typhoid fever (Salmonella typhi): The most commonly used vaccine contains an attenuated recombinant strain of S. typhi. It is given to individuals living in or traveling to high-risk areas and to members of the military.
4. Plague (Yersinia pestis): The vaccine contains killed bacteria and is given to high-risk individuals.

VIRAL VACCINES

Immunity to viral infection requires an immune response to antigens located on the surface of the viral particles or on virus-infected cells. For enveloped viruses, these antigens are often surface glycoproteins. Common viral pathogens for which there are vaccines include the following.

A. Hepatitis A

Formalin-inactivated whole virus vaccine produces antibody levels in adults similar to those observed following natural infection and approximately 15 times those achieved by passive injection of immunoglobulin. Projections indicate that immunity to hepatitis A virus will probably last for approximately 10 years after two doses of vaccine. The vaccine is indicated for travelers to endemic areas, men who have sex with men, injecting drug users, and daycare workers.

B. Hepatitis B

The current vaccine contains recombinant hepatitis surface antigen. Efficacy is 95 to 99 percent in healthy infants, children, and young adults. Its use is indicated for healthcare workers in contact with blood and persons residing in an area with a high rate of endemic disease. Igs obtained from hyperimmunized humans can provide passive immunity after accidental exposure.

C. Varicella zoster

This vaccine contains live, attenuated, temperature-sensitive varicellazoster virus. Its efficacy in preventing chickenpox is approximately 85 to 100 percent in children, and this immunity is persistent. Anti-varicella-zoster Ig provides passive immunity for immune-compromised individuals at risk of infection.

D. Polio

Vaccination is the only effective method of preventing poliomyelitis. Both the inactivated polio vaccine and the live, attenuated, orally administered polio vaccine have established efficacy in preventing poliovirus infection and paralytic poliomyelitis.

1. Inactivated poliovirus (Salk) vaccine: Because the inactivated vaccine cannot cause poliomyelitis, it is safe for use in immune-compromised persons and their contacts. The disadvantages of this inactivated vaccine are: 1) administration is by injection only, and 2) it provides less GI immunity, resulting in the possibility of asymptomatic infection of the GI tract with wild poliovirus, which could be transmitted to other persons.

2. Attenuated live poliovirus (Sabin) vaccine: Advantages of this vaccine include: 1) it can be administered orally, 2) it provides life- long protection from poliovirus for more than 95 percent of recipients after the primary three-dose series, and 3) it provides early GI immunity.

E. Influenza

The traditional “flu shot” vaccine contains formalin-inactivated virus. A live, attenuated influenza vaccine is administered intranasally. The vaccine provides peak protection about 2 weeks after its administration. Vaccine efficacy of 70 to 90 percent is generally achieved in young adults.

F. Measles, mumps, and rubella This combination vaccine contains live, attenuated virus and should be administered to young children prior to entering school. Measles vaccine should also be administered to individuals traveling in endemic areas.

J. Human papillomavirus vaccine

Human papillomavirus (HPV) vaccine is recommended for routine administration in all children beginning at ages 11 to 12 years.

DNA VACCINES

DNA vaccines represent a new approach to vaccination. The proposed mechanism for these vaccines is that the gene for the antigen of interest is cloned into a bacterial plasmid, which is engineered to increase the expression of the inserted gene in mammalian cells.

OVERVIEW OF ANTIMICROBIAL AGENTS

Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity (that is, they have the ability to kill or inhibit the growth of an invading microorganism without harming the cells of the host).

AGENTS USED TO TREAT BACTERIAL INFECTIONS

The clinically useful antibacterial drugs are organized into six families: penicillins, cephalosporins, tetracyclines, aminoglycosides, macrolides, and fluoroquinolones, plus a seventh group labeled “other” used to represent any drug not included in one of the other six drug families.

A. Penicillins

Penicillins are β-lactam antibiotics, named after the β-lactam ring that is essential to their activity. Penicillins selectively interfere with the synthesis of the bacterial cell wall, a structure not found in mammalian cells. Penicillins are inactive against organisms devoid of a peptidoglycan cell wall, such as mycoplasma, protozoa, fungi, and viruses.

B. Cephalosporins

Cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins, and they are also bactericidal. Cephalosporins have the same mode of action as the penicillins, but they tend to be more resistant than the penicillins to inactivation by β-lactamases produced by some bacteria.

C. Tetracyclines

A number of antibiotics, including tetracyclines, aminoglycosides, and macrolides, exert antimicrobial effects by targeting the bacterial ribosome, which has components that differ structurally from those of the mammalian cytoplasmic ribosomes. Binding of tetracyclines to the 30S subunit of the bacterial ribosome is believed to block access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site, thereby inhibiting bacterial protein synthesis.

D. Aminoglycosides

Aminoglycosides inhibit bacterial protein synthesis. Susceptible organisms have an oxygen-dependent system that transports the antibiotic across the cell membrane. All aminoglycosides are bactericidal. They are effective only against aerobic organisms because anaerobes lack the oxygen-requiring transport system.

E. Macrolides

Macrolides are a group of antibiotics with a macrocyclic lactone structure. Erythromycin was the first of these to find clinical application, both as the drug of first choice and as an alternative to penicillin in individuals who are allergic to β-lactam antibiotics. The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thereby inhibiting the translocation steps of protein synthesis.

F. Fluoroquinolones

Fluoroquinolones uniquely inhibit the replication of bacterial DNA by interfering with the action of DNA gyrase (topoisomerase II) during bacterial growth. Binding quinolone to both the enzyme and DNA to form a ternary complex inhibits the rejoining step, and, thus, can cause cell death by inducing cleavage of the DNA.

G. Carbapenems

Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins. Imipenem, meropenem, doripenem, and ertapenem are the drugs of this group currently available. Imipenem is compounded with cilastatin to protect it from metabolism by renal dehydropeptidase. Imipenem resists hydrolysis by most β-lacta- mases. Meropenem and doripenem have antibacterial activity similar to that of imipenem. However, ertapenem is not an alternative for P. aeruginosa coverage because most strains exhibit resistance. Ertapenem also lacks coverage against Enterococcus species and Acinetobacter species.

H.Other important antibacterial agents

1. Vancomycin: inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization at a site earlier than that inhibited by β-lactam antibiotics. Vancomycin is useful in patients with serious allergic reactions to β-lactam antibiotics and who have gram-positive infections.

2. Trimethoprim-sulfamethoxazole: A combination called co-trimoxa- zole shows greater antimicrobial activity than equivalent quantities of either drug used alone. The synergistic antimicrobial activity of co-trimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid: sulfamethoxazole inhibits incorporation of PABA into folic acid, and trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate.

DRUG RESISTANCE

Bacteria are said to be resistant to an antimicrobial drug if the maximal level of the agent that can be achieved in vivo or tolerated by the host does not halt their growth. Some organisms are inherently resistant to an antibiotic, for example, because they lack the target of the antimicrobial agent. However, microbes that are normally responsive to a particular drug may develop resistance through spontaneous mutation or by acquisition of new genes followed by selection.

A. Genetic alterations leading to drug resistance

Acquired antibiotic resistance involves mutation of existing genes or the acquisition of new genes.

1. Spontaneous mutations in DNA: Chromosomal alteration may occur by insertion, deletion, or substitution of one or more nucleotides within the genome. The resulting mutation may persist, be corrected by the organism, or be lethal to the cell. If the cell survives, it can replicate and transmit its mutated properties to progeny cells.

2.DNA transfer of drug resistance: Of particular clinical concern is resistance acquired due to DNA transfer from one bacterium to another. Resistance properties are often encoded on extra-chromosomal plasmids, known as R, or resistance, factors. DNA can be transferred from donor to recipient cell by processes including transduction (phage mediated), transformation, or bacterial conjugation.

B. Altered expression of proteins in drug-resistant organisms

Drug resistance may be mediated by several different mechanisms, including an alteration in the antimicrobial drug target site, decreased uptake of the drug due to changes in membrane permeability, increased efflux of the drug, or the presence of antibiotic-inactivating enzymes.

1. Modification of target sites: Alteration of an antimicrobial agent's target site through mutation can confer resistance to one or more related antibiotics.

2. Decreased accumulation: Decreased uptake or increased efflux of an antimicrobial agent can confer resistance because the drug is unable to attain access to the site of its action in sufficient concentrations to inhibit or kill the organism.

3. Enzymatic inactivation: The ability to destroy or inactivate the antimicrobial agent can also confer resistance to microorganisms.

AGENTS USED TO TREAT VIRAL INFECTIONS

When viruses reproduce, they use much of the host’s own metabolic machinery. Therefore, few drugs are selective enough to prevent viral replication without injury to the host. Viruses are also not affected by antibacterial agents. Nevertheless, some drugs sufficiently discriminate between cellular and viral reactions to be effective and yet relatively nontoxic.

A. Organization of viruses

The clinically important viruses can be conveniently divided into seven groups based on the nature of their genome, symmetry of organization, and the presence or absence of a lipid envelope.

B. Treatment of herpesvirus infections

Most antiviral agents used in treating herpesvirus infections are nucleoside analogues that require conversion to mono-, di-, and triphosphate forms by cellular kinases, viral kinases, or both to selectively inhibit viral DNA synthesis.

C. Treatment of acquired immunodeficiency syndrome

Antiretroviral drugs are divided into five main classes based on their mode of inhibition of viral replication. The first class represents nucleoside analogs that inhibit the viral RNA–dependent DNA polymerase (reverse transcriptase) of HIV. A second class of reverse transcriptase inhibitors includes non-nucleoside analogs. The third class includes protease inhibitors. The fourth class is a fusion inhibitor that prevents HIV from entering the host cell. The fifth class, integrase inhibitors, blocks the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell. Therapy with these antiretroviral agents, usually in combinations (a “cocktail” of drugs referred to as highly active antiretroviral therapy, or HAART), is beneficial to prolong survival, to reduce the incidence and severity of opportunistic infections in patients with advanced HIV disease

D.Treatment of viral hepatitis

Prolonged (months) treatment with interferon-α has succeeded in reducing or eliminating indicators of hepatitis B virus replication in about one third of patients.

The therapy of choice for hepatitis C is interferon-α in combination with ribavirin. The overall rate of response to this drug combination is three times greater than that seen with interferon-α monotherapy. However, anemia is a common adverse effect induced by ribavirin.

E. Treatment of influenza

Zanamivir and oseltamivir are effective against influenza A and B. They inhibit viral neuraminidase, thereby preventing the release of virus from infected cells.

CHAPTER 6
Bacterial Structure, Growth, and Metabolism

Overview

The cellular world is divided into 2 major groups: if the cells have nucleus it called eukaryotes, and if the cells lack a nucleus it called prokaryotes. All bacteria are prokaryotic. The eukaryotic DNA is a single double strand molecule of DNA. Prokaryotic and eukaryotic cells have a very similar metabolic pathway to achieve cell growth and maintain viability. However, prokaryotes synthesize substances and structures that are unique to bacteria.

THE CELL ENVELOPE

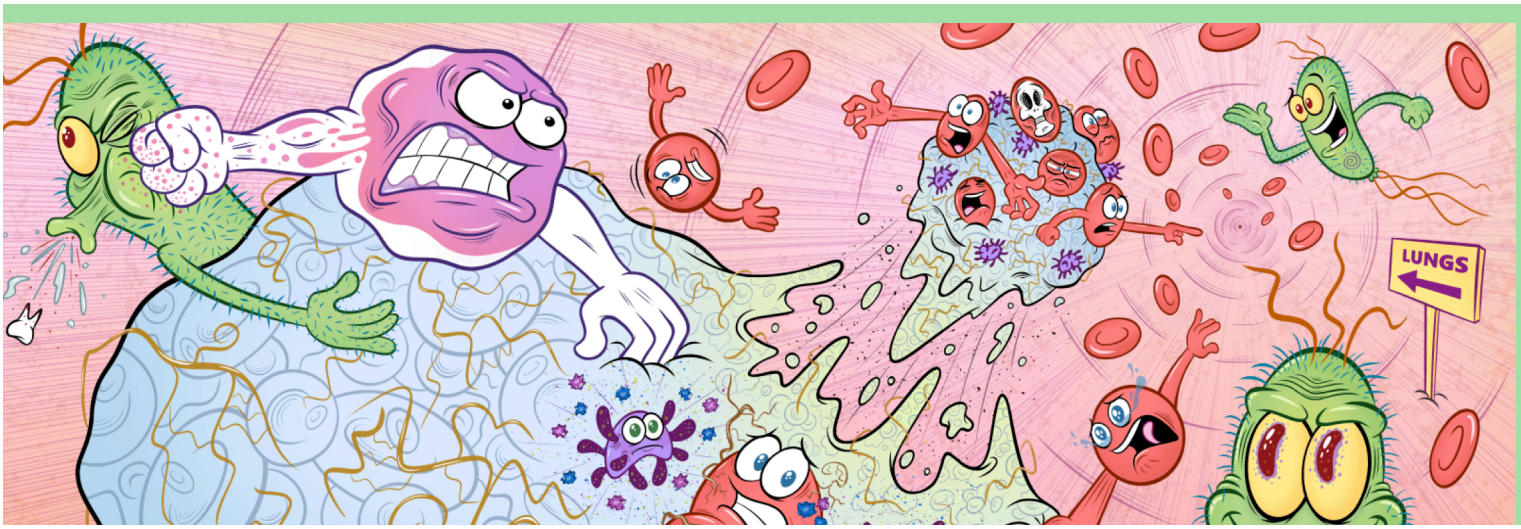
The bacterial "cell envelope" is all material external to and enclosing the cytoplasm. It consists of several chemically and functionally distinct layer, the most prominent of which are the cell wall, cytoplasmic membrane, and the capsule or glycocalyx, if present.

A. Cytoplasmic membrane

The cell membrane is composed of phospholipid, the molecules of which form two parallel surfaces (called a lipid bilayer). The membrane acts as a permeability barrier, control the amount of molecules that enter and leave the cell.

B. Peptidoglycan

The peptidoglycan layer determines the shape of the cell. It is composed of a cross-linked polymeric mesh. The glycan portion is composed of N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM). This polymer is the carbohydrate "backbone" of the mesh. The "peptido" portion is a short string of amino acids that attached to the NAM subunits of the backbone, forming a network with high tensile strength.



Differences between gram-positive and gram-negative cell walls

1-Gram - positive organism	2- Gram - negative organism
1-Have thick multilayered peptidoglycan cell walls 2-The peptidoglycan is covalently linked to teichoic acid (a polymer of substituted glycerol units linked by phosphodiester bonds). 3-The teichoic acids are major cell surface antigens. 4-Teichoic acids are integrated into the peptidoglycan layers.	1-The peptidoglycan layer of gram-negative cells is thin, so the cell is liable to physical damage. 2-Have two membranes (an outer membrane and an inner, that is, cytoplasmic, membrane). 3-Have periplasmic space: found between the inner and outer membrane , and its contains the peptidoglycan layer , degradative enzymes and transport proteins. 4- The outer membrane has lipopolysaccharide (LPS). 5- The polysaccharide portion of LPS is antigenic and the lipid portion (called lipid A) is imbedded in the membrane and is toxic to humans and animals. 6- Lipid A is an integral part of the membrane.

D. The external capsule and gycocalyx:

Many bacteria secrets a sticky viscous material form a cote for the cell. Is composed of polysaccharide. However, in case of Bacillus anthracis, the capsule is composed of poly-D glutamatic acid. If the material is tightly bound to the cell we called it Capsule. If it loosely bound it's called slime layer, or glycocalyx. They allow the cells to adhere to surfaces, protection from antibodies, phagocytosis, and act as diffusion barriers against some antibiotics.

E. Appendages: There are of two kinds of appendages:

1.flagella (singular, flagel- lum) الأسواط:

Long, semirigid, helical, hollow tubular structures composed of several thousand molecules of the protein flagellin. They enable bacteria to move in a directed fashion. Cells may have one or many flagella. Flagella are highly antigenic.

2.Pili (singular, pilus) الأهداب:

(Sometimes called fimbriae) are shorter and thinner than flagella and function as attachment structures that promote cell-to-cell contact.

F. Antigenic variation:

Is the expression of various alternative forms of antigen on the cell surface. Most surface structures are subject to antigenic variation, including LPS, capsules, lipoteichoic acids, pili, and flagella. This variation is important for immune evasion by the pathogen.

G. SPORES AND SPORULATION:

When the bacterial cell goes under harsh environmental conditions such as nutritional deprivation, some of these bacteria have the ability to form what's called spores. It uses to enhance survival during that period. Spores are the most resistant life forms known. They come from the original cells.

A. Sporulation

Sporulation can be thought of as repackaging a copy of bacterial DNA into a new form that contains very little water, has no metabolic activity, does not divide, and has a restructured, highly impermeable, multilayered envelope.

B. Spore germination

To return to the vegetative state, spores must first be subjected to a treatment that weakens the spore coat (such as heat or extremes of pH), thus allowing germination to occur. This process involves destruction of the cortex by lytic enzymes, followed by uptake of water, and release of calcium dipicolinate from the cell.

B. **Medical significance of sporulation**

Some of the most notorious pathogens are spore-formers, including: Clostridium tetani , Clostridium botulinum ,and Clostridium difficile . Spores of these organisms can remain viable for many years and are gener- ally not killed by boiling, but they can be killed by autoclaving (that is, subjecting the spores to temperatures above 120oC at elevated pressure). In the absence of an autoclave, spores can be largely eliminated by a primary boiling to activate germination and, after a short period of vegetative growth, a second boiling.

C.

GROWTH AND METABOLISM

Bacterial or human, have similar metabolic pathways. However, there are some important differences that set bacteria apart metabolically from eukaryotic cells.

A. Characteristics of bacterial growth:

If bacterial cells are suspended in a liquid nutrient medium, the increase in cell number or mass can be measured in several ways. Techniques include microscopically counting the cells in a given volume using a ruled slide, counting the number of appropriately diluted cells that are able to form colonies following transfer to a solid nutrient (agar) surface.

1. Stages of the bacterial growth cycle: Bacteria reproduce by binary fission, the number of cells increases exponentially with time . Depending on the species, the minimum doubling time can be as short as 10 minutes or as long as several days. For example; a single cell of E.coli can give rise to some 10 million cells in just 8 hours.

2. Surface growth colony: is compact macroscopic mass of cells, each colony contains millions of cells. The gross characteristics of colonies can be useful guides for identification of the species of bacterium.

B. Energy production:

There are a variety of mechanisms used to generate energy from carbon sources. Depending on the biochemical mechanism used, bacterial metabolism can be divided into three types: aerobic respiration, anaerobic respiration, and fermentation.

1. Aerobic respiration

Requires oxygen molecules to generate energy.

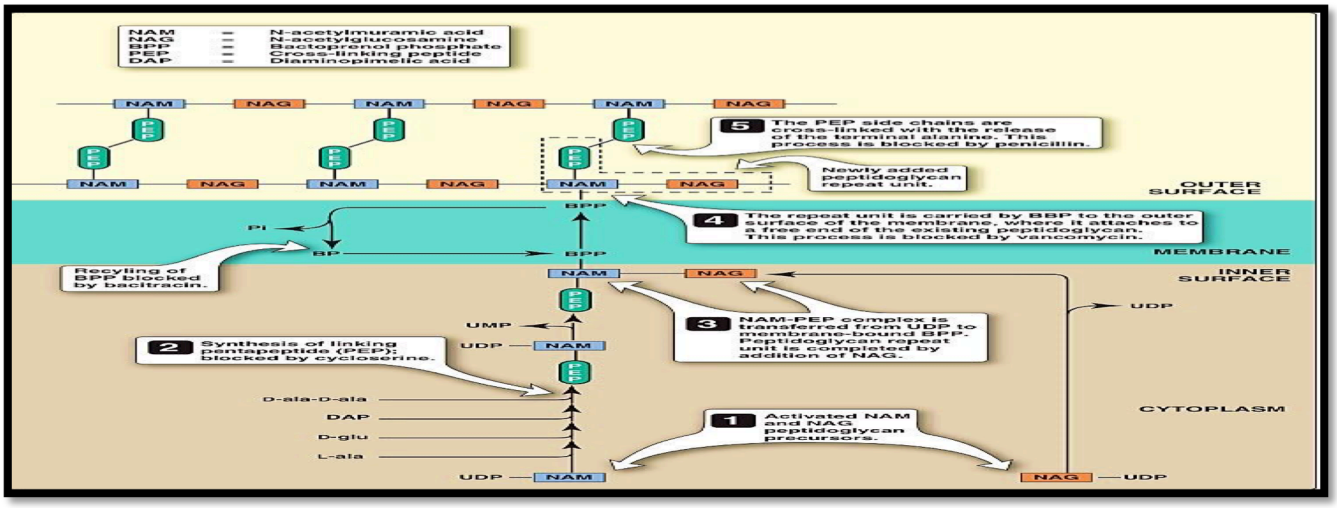
2.Anaerobic respiration

Requires inorganic compounds other than molecular oxygen to generate energy.

3. Fermentation

Is an anaerobic process utilized by some bacterial species. It is the metabolic process by which an organic metabolic intermediate derived from a “fermentable” substrate serves as the final electron acceptor.

C. Peptidoglycan synthesis:



Is constructed on the surface of the cell membrane and is composed of a repeating carbohydrate backbone subunit, which is (NAG–NAM). These backbone chains are cross-linked by short peptides (PEP) to form a rigid meshwork. Peptidoglycan biosynthesis occurs via the following series of steps.

Peptidoglycan biosynthesis as a target of some antibacterial agents: cell wall synthesis is an ideal target for some specific antibacterial agents, particularly theβ-lactam antibiotics.

a. β- Lactam antibiotics: Penicillins and cephalosporins inhibit the enzymes that catalyze transpeptidation and carboxypeptidation reactions of cell wall assembly. These enzymes are called peni- cillin-binding proteins (PBPs) because they all have active sites that bind β-lactam antibiotics.

b. Bacitracin, cycloserine, and vancomycin: Other antibiotics that interfere with peptidoglycan synthesis include bacitracin, which inhibits the recycling of bactoprenol phosphate, cycloserine, which inhibits synthesis of the D–ala–D–ala dipep- tide that provides the two terminal residues of the pentapep- tide, and vancomycin , which blocks incorporation of the NAG–NAM–PEP repeat unit into the growing peptidoglycan chain

CHAPTER 7

BACTERIAL GENETICS

GENOME

The total of genetic material of a cell. Consists of a single chromosome that carries all of the essential genes and one or more varieties of plasmid that generally carry nonessential genes.

BACTERIOPHAGE

A bacteriophage (phage) is a virus that replicates inside a bacterial cell. It consists of nothing more than a piece of nucleic acid encapsulated in a protective protein coat. Depending on the phage, the nucleic acid can be DNA or RNA, double stranded or single stranded.

REPLICATION OF BACTERIOPHAGE:

When virus enter the cell there is tow pathways can be taken:

1- Lytic cycle (Virulent phage- Temperate phage).

2- Lysogenic cycle.

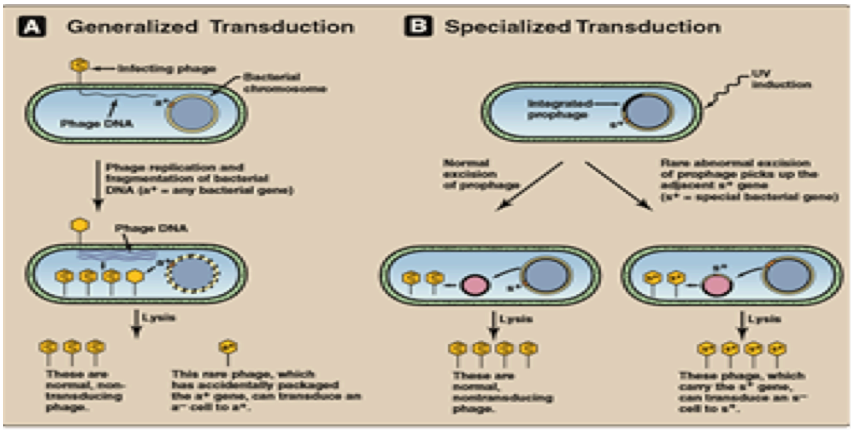
GENE TRANSFER:

A. Conjugation

Conjugation is the process by which bacteria transfer genes from one cell to another by cell-to-cell contact. The donor (male) and recipient (female). The process requires the presence on the donor cell of a hair like projection called a sex pilus to exchange the genetic material.

B. Transduction

Transduction refers to transfer of genes from one cell to another via a phage vector without cell-to-cell contact. There are two ways in which this can occur: generalized transduction and specialized transduction.



C. Transformation

Transformation is the transfer of genes from one cell to another by means of naked DNA.

GENETIC VARIATION:

A. Mutations

Strictly speaking, any change in the structure of genetic material or, more specifically, any change in the base sequence of DNA, is called a mutation.

B. Mobile genetic elements

In recent years, it has been recognized that the arrangement of genes in the genome of bacteria is not entirely static. Certain DNA segments, called transposons, have the ability to move from place to place on the chromosome and into and out of plasmids.

C. Mechanisms of acquired antibiotic resistance.

Acquired antibiotic resistance requires a temporary or permanent gain or alteration of bacterial genetic information. Although most resistance genes are plasmid mediated, plasmid-mediated traits can interchange with chromosomal elements. Transfer of genetic material from plasmid to chromosome can occur by simple recombinational events. Resistance to antibiotics is accomplished by five principal mechanisms:

1. Decreased uptake of antibiotic.
2. Antibiotic efflux.
3. Alteration of the target site for antibiotic.
4. Acquisition of the ability to destroy or modify the antibiotic.
5. Acquisition of a new target.

GENE REGULATION:

Bacteria have evolved various mechanisms for producing certain metabolic enzymes only when they are needed. Most regulation in bacteria involves control of transcription, rather than control of translation of the mRNA into protein.

A. Negative control (repression).
B. Positive control (activation).
C. Modifications of RNA polymerase specificity (switch on or off)

Chapter 8

Staphylococci

Staphylococci:

Are Gram-positive pyogenic cocci arranged in grape like clusters.

Morphology and Characteristics:

1.Gram-positive. 2. Non-motile.

3. Non-spore forming. 4.Facultative anaerobes.

5. Catalase Positive. 6.Salt tolerant.

7. Resistant to drying. 8.Adapted to survival on the skin.

9- Present as normal flora.

Classification of Staphylococcus:

1-Staphylococcus Aureus.

2-Coagulase-Negative Staphylococci.

STAPHYLOCOCCUS AUREUS:

A. Epidemiology.

S.aureus is frequently carried by healthy individuals on the skin and mucous membranes. Carriers serve as a source of infection to them- selves and others; for example, by direct contact or contamination of food, which can then result in food poisoning.

B. Pathogenesis.

Virulence factors are the genetic, biochemical, or structural features that enable an organism to produce disease.

Virulence Factors:

1. Cellular Antigens(cell-associated).		2. Extra-cellular (released from cell).
Capsules:	**Prevents phagocytosis.**	**Enzymes**
Cell wall polymers:	**Peptidoglycan and Teichoic acid.**	**Toxin**
Cell surface proteins:	**Protein A. Reacts with Fc region of IgG. Prevents antibody mediated clearance.**	

Extra-cellular antigens:

Toxins	Action / effect
Hemolysins a, b, g & δ toxins	Destroy RBC, neutrophils, macrophages & platelets. a-toxin very important. Damages skin & muscle cells. B-toxin known as hot cold toxin.
Exfoliatin (exfoliative toxin)	Causes blistering of skin. Important in scalded skin syndrome.
Enterotoxins (A-E, G,H & I).	Increases intestinal peristalsis and fluid loss. Cause diarrhea / vomiting.
Toxic shock syndrome toxin (TSST).	Super antigen. Releases large amounts IL-1, IL2 & TNF. Multisystem effect.
Leucocidin.	Destroys leucocytes.

C. Clinical significance:

A) Disease caused by exotoxin release:

1. Gastroenteritis (Food Poisoning).
2. Toxic Shock syndrome.
3. Scalded Skin Syndrome.

B) Disease resulting from direct organ invasion:

1. Localized skin infections.

2. Deep, localized infections.

3. Acute endocarditis. التهاب شغاف القلب

4. Septicemia. تعفن الدم

5. Pneumonia. الألتهاب الرئوي

6. Nosocomial infections. عدوة المستشفيات

D. Treatment:

S.aureus infections require aggressive treatment, including incision and drainage of localized lesions, as well as systemic anti - biotics. Choice of antibiotics is complicated by the frequent presence of acquired antibiotic resistance.

1. Hospital-acquired methicillin-resistant S. aureus (MRSA).

2. Community-acquired MRSA (CA-MRSA).

3. Vancomycin resistance.

E. Prevention:

There is no effective vaccine against S.aureus .Infection control procedures, such as barrier precautions and disinfection of hands.

COAGULASE-NEGATIVE STAPHYLOCOCCI:

A. Staphylococcus epidermidis

S.epidermidis is present in large numbers as part of the normal flora of the skin. Generally as a contaminant from skin. Despite its low virulence, it is a common cause of infection of implants such as heart valves and catheters.

B. Staphylococcus saprophyticus this organism is a frequent cause of cystitis in women, probably related to its occurrence as part of normal vaginal flora. It tends to be sensitive to most antibiotics.

CHAPTER 9

Streptococci

Streptococci:

1.Gram positive cocci.

2.Catalase negative.

3. Non-motile Non-sporing.

4.Often require enriched media “blood agar”.

5.Facultative anaerobes.

6.Arranged in chains (Strept. Pyogenes) or pairs (Strept. Pneumoniae).

CLASSIFICATION OF STREPTOCOCCI:

Streptococci can be classified by several schemes, for example, by the hemolytic properties of the organisms, and according to the presence of specific surface antigens determined by immunologic assays.

Streptococcus :

1-β-hemolytic

Complete hemolysis They form a clear zone around their colonies because complete lysis of the RBCs occurs (in the blood agar plate). B-hemolytic are classified alphabetically by Lancefield according to possession of Carbohydrate antigens (polysaccharide) in the cell wall.

2- α-hemolytic.

Partial hemolysis forms a green zone around their colonies as a result of incomplete lysis of RBCs in blood agar.

3- Non-hemolytic (Gamma hemolytic).

Are unable to hemolysis RBCs & have no effect on blood agar.

β-hemolytic strept:

A- GROUP A : Streptococcus pyogenes:

Pathogenicity: It causes disease by 3 mechanisms:

1) Inflammation (pharyngitis).

2) Exotoxin release and enzyme production.

3) Immunologic mechanism (Rheumatic Fever).

B- Structure and physiology:

1. Capsule: Hyaluronic acid antiphagocytic.
2. Cell wall: M protein : surface proteins which act as anti-phagocytic factors.
3. Extracellular products: S. pyogenes secretes a wide range of exotoxins that often vary from one strain to another and that play roles in the pathogenesis of disease.

C-Epidemiology: The only known reservoir for S. Pyogenes in nature is the skin. Spreads group A streptococcal infection from person to person, especially in crowded environments.

D- Clinical significance: S. pyogenes is a major cause of cellulitis. Other more specific syndromes include:

1. Acute pharyngitis or pharyngotonsilitis.
2. Impetigo.مرض جلدي يسمى القوباء
3. Erysipelas.التهاب جلدي
4. Puerperal sepsis. حمى النفاس
5. Streptococcal toxic shock syndrome.
6. Post-streptococcal sequelae.
7. Acute rheumatic fever.
8. Acute glomerulonephritis,التهاب كلوي حاد

E-Laboratory identification:

Specimens: from infected sites (e.g. tonsillitis= throat swab, skin).

•Microscopy: Gram positive cocci arranged in chains.

•Culture: Beta-hemolysis on BAP (blood agar plate) – sensitive to bacitracin.

•Biochemical tests: Catalase-negative.

•Lancefield Grouping: A .

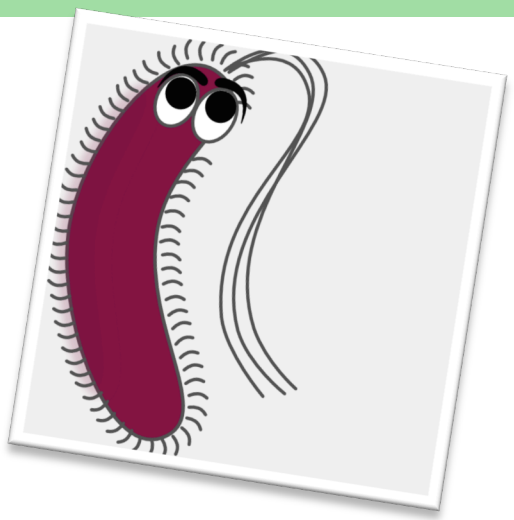
F- Treatments:

-Penicillin G: drug of choice for treatment of infection by group A β-hemolytic.

-Erythromycin: for penicillin-allergic patients.

CHAPTER 10

Gram-positive rods



A. Corynebacteria

- Gram-positive rods, stain unevenly, small, slender, pleomorphic.

- Characteristic clumps look like Chinese characters (palisade arrangement).

- Non motile, unencapsulated , do not form spores.

- Most species are facultative anaerobes but, Corynebacteria diphtheria is aerobic.

B. Corynebacteria diphtheriae مرض الدفتيريا هو إلتهاب تنفسي حاد

Life threatening disease start as local infection in the throat , acute respiratory disease .

1.Epidemiology:

-Found in the throat & nasopharynx of convalescent or asymptomatic carriers

- spread by respiratory droplets[1] , highly contagious.

2- Pathogenesis:

- Caused by local & systemic effects of a single exotoxin that inhibits eukaryotic protein synthesis .

- The toxin inactivates eukaryotic polypeptide chain elongation factor EF-2 by ADP-ribosylation[2].

- Toxin is encoded on Beta- Corynephage into chromosome produce toxin.

- Environment regulate the toxin gene, low iron condition induce toxin expression but, high iron repress toxin production.

3- Clinical significance:

a-Upper respiratory tract infection a local infection in the throat , produce distinctive thick grayish adherent exudate[3] , obstruct airway leads to suffocation.

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[1] Less frequently spread by direct contact with infected person.
[2] Toxin is heat labile polypeptide & composed of 2 fragments , inside the cell one of fragment catalyzes a reaction between NAD+ & eukaryotic polypeptide chain elongation factor.
[3] Pseudomembrane is composed of cell debris from the mucosa & inflammatory product.

-Cardiac defect & myocarditis lead to congestive heart failure, Neuritis of cranial nerves & paralysis of muscles.

b-Cutaneous diphtheria a puncture wound in skin , chronic , non healing ulcer with gray membrane .Tissue degeneration & death caused by exotoxin production.

4- Immunity:

-Diphtheria toxin is antigenic & stimulated production of antibodies that neutralize toxin[4].

5-Laboratory identification:

-Initial diagnosis based on clinical observation[5] & a definitive diagnosis by test virulence[6].

-Tinsdale agar media contains potassium tellurite , an inhibitor of other respiratory flora.

-Culture morphology is distinctive black colonies with halos , then stain with methyleneldue appears bands &reddish granules[7].

-Immunologic precipitin reaction test for toxin production.

6-Treatment:

-Single dose of antitoxin inactivates circulating toxin but does not affect toxin that is already bound to a cell surface receptor.

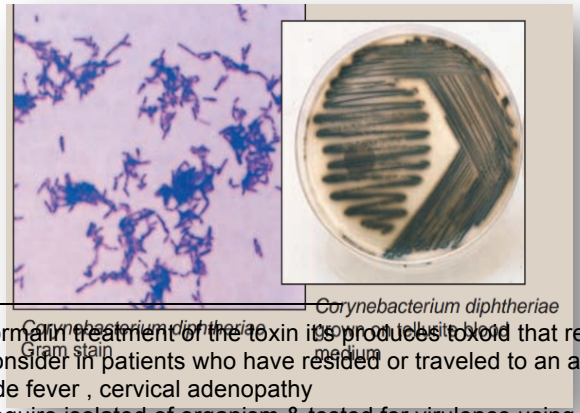
-Eradication the organism by Erythromycin or Penicillin G.

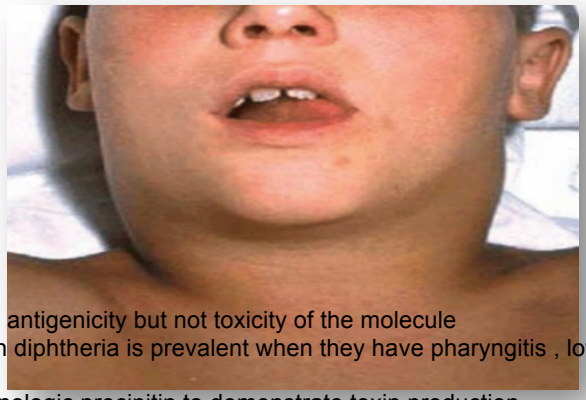
7-Prevention:

-Immunization with toxoid in DTaP triple vaccine.

- Should be started in infancy.

-Booster injections of diphtheria toxoid[8] should be given approximately at 10 years intervals throughout life.





[4] Formalin treatment of the toxin its produces toxoid that retains the antigenicity but not toxicity of the molecule
[5] Consider in patients who have resided or traveled to an area which diphtheria is prevalent when they have pharyngitis , low grade fever , cervical adenopathy
[6] Require isolated of organism & tested for virulence using an immunologic precipitin to demonstrate toxin production
[7] Polychromatic
[8] With tetanus toxoid

I.Bacillus Species

-Gram positive rods , form endospores ,antiphagocytic.

-Either strict aerobes or aerotolerant anaerobes.[9]

-Found in soil, water, airborne contaminates.

A.Bacillus anthracis انسان الى وينتقل دمويا إنتانا يسبب الماشية في هومرض الخبيثة الجمرة

1.Epidemiology:

-Enzootic disease [10], affects domestic herbivores , highly resistant to physical & chemical agent.

-Transmitted by contact with infected animals products ,contaminated dust.

-Initiated by the subcutaneous inoculation of spores in skin abrasions.

-Inhalation causes a pulmonary form of anthrax.

-The spores remain viable for many years in contaminated pastures & animal material.

2.Pathogenesis:

-Produces a unique capsule that is comprised of poly-D-glutamic acid , antiphagocytic , full virulence.

-Produces two plasmid coded exotoxins : edema toxin & lethal toxin , both are AB type with activity & binding[11] domains.

-Edema factor[12]is a calmodulin dependent adenylyl cyclase causes elevation of intracellular cAMP leading to sever edema.

-Lethal factor disrupts cellular signalling &induces cytokines lead to tissue necrosis.

3.Clinical significance:

A.Cutaneous anthrax: painless, black , severely swollen " malignant pustule" , invade lymph nodes then general circulation leading to fatal septicemia , some cases remain localized &heal.

B.Pulmonary anthrax (woolsorter's disease): caused by inhalation of spores characterized by progressive hemorrhagic lymphadenitis [13], hemorrhagic mediastinitis[14] , mortality rate 100%.

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[9] Note: can grow in present of oxygen but don't require it
[10] Disease in animals population
[11] The binding subunit shared by both toxins is called protective antigen
[12] Activity subunits are called edema factor& lethal factor
[13] Inflammation of lymph nodes
[14] Inflammation of mediastinum

4.Laboratory Identification:

-Blunt ended bacilli that occur singly in pairs or frequently in long chains , they don't sporulate in clinical samples but do so in culture

-The spores are oval & centrally located , on blood agar the colonies are large , grayish , nonhemolytic with irregular border nonmotile[15] & encapsulated in vivo, identification of organism by a direct immunofluorescence assay.

5.Treatment:

● Cutaneous anthrax → Ciprofloxacin.

●Pulmonary anthrax (woolsorter's disease) multidrug therapy is recommended → Ciprofloxacin , Rifampin , Clindamycin or Ciprofloxacin , Rifampin , Vancomycin.

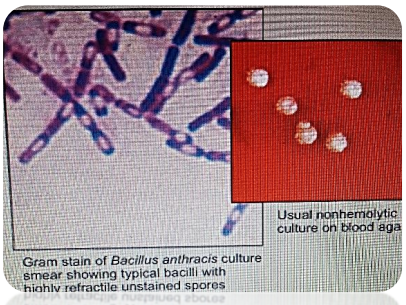
6.Prevention:

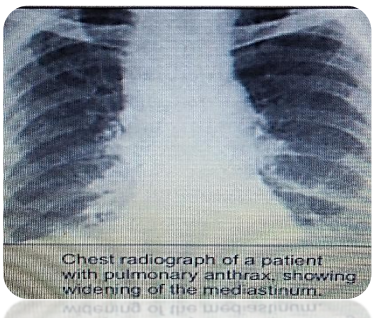
-A cell free vaccine is available for workers in high risk occupations , postexposure prophylaxis with Ciprofloxacin or Doxycycline is recommended [16].

II. Other bacillus species:

-Are implicated in opportunistic lesions or following trauma or placement of artificial devices.

-A commonly identified species is Bacillus cereus[17]produce a tissue destructive exotoxin.





[15] Unlike many bacillus species B.anthracis is non motile
[16] Cause of resistance of endospores
[17] Causes food poisoning by enterotoxin

I. Listeria

- Short, slender, gram positive rods, don't form spores , occur as diplobacilli or short chains , catalase positive , distinctive tumbling motility[18] facultative intracellular parasites , grow in variety of enriched media.

●Listeria monocytogenes[19] داء الليستريات , الليسترية المستوحدة

1.Epidemiology:

-Only species that infects humans, transmitted by foodborne , asymptomatic carriers , infection is common in pregnant women , fetuses , newborn , immunocompromised[20].

2.Pathogenesis:

-The organism attaches to & enters a variety of mammalian cells[21] once internalized it escapes by producing a membrane-damaging toxin called listeriolysin O.

-Grow in the cytosol & utilizes actin based motility & the protein ActA to facilitate its direct passage from cell to cell[22].

2.Clinical significance:

-Listeriosis septicemia & meningitis are the most common forms of infection, in pregnant can be transmitted to the fetus result in spontaneous abortion [23]or to newborn result in neonatal meningitis, immunocompromised [24]are susceptible to serious generalized infections.

3.Laboratory identification:

-On blood agar a small colony surrounded by a narrow zone of Bata- hemolysis.

4.Treatment & Prevention:

- Treat infection by Ampicillin[25]& Trimethoprim / Sulfamethoxazole[26].

-Prevention by proper food preparation & handling, removal of contaminated products from the food.

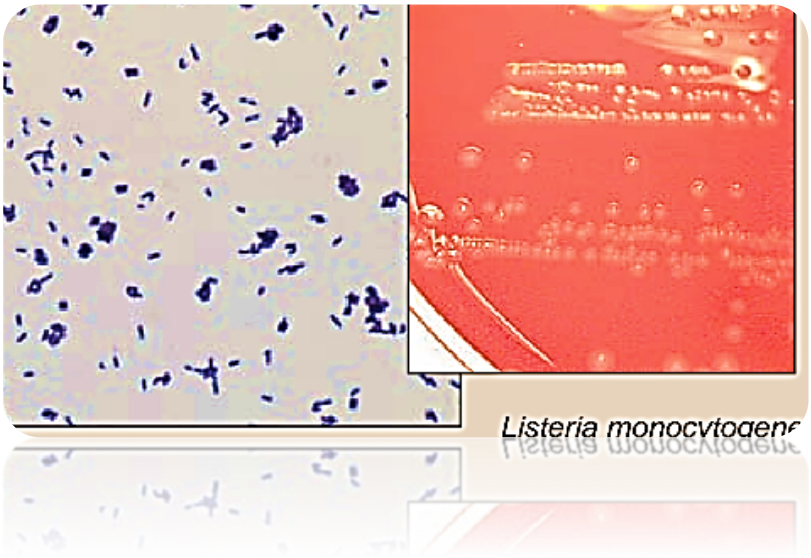
II. Other non-spore-forming gram positive rods

[18] In light microscopy in liquid medium which is most active after growth at 25°C
[19] Capable of growth in 4°C
[20] Such as older adult, patient who received corticosteroids
[21] By normal phagocytosis
[22] Induce a reorganization of cellular actin such as short filaments & actin binding proteins adhere to the bacteria look like "tail", bacterium produce membrane degrading phospholipases
[23] From asymptomatic vaginal colonization
[24] Especially with defects in cellular immunity
[25] First line drugs
[26] Alternative drugs

-Propionibacterium is anaerobic[27] ,common inhabitants of normal skin cause endocarditis & infection in plastic implants. P. acnes a strict anaerobe cause of acne.

- Lactobacillus are part of the mucous membrane flora, produce lactic acid during fermentation & maintain the acid pH, acid production may progression of dental caries.

- Erysipelothrix rhusiopathiae is filamentous, gram positive rod causes disease in animals[28]



[27] Or microaerophilic rods of diphtheroidlike morphology
[28] Erysipeloid a skin infection in who commonly handle animal products

CHAPTER 11

Gram Negative Cocci

I.Neisseria Gonorrhoeae

- Gram negative diplococcus , anaerobic , oxidase positive , like kidney shape , unencapsulated , piliated , nonmotile , transmitted during sexual contact , through infected birth canal [29].

1. Stucture:

- Pili[30]: hair like surface appendages &made of helical aggregates of repeating peptide subunits called pilin.

-Lipooligosaccharide [31]: shorter, highly branched , nonrepeat O-antigenic side chains.

-Porin protein: expresses a single porin type known as PorB.

-Opacity protein have tendency to impart an opaque quality [32] numerous polymeric repeats.

2.Pathogenesis:

-Pili & Opa protein facilitate adhesion to epithelial cells[33] , produce an IgA protease that cleaves IgA, acquires necessary nutrient by expression of specific transport systems that remove & internalize the iron from human iron binding proteins include transferrin ,lactoferrin,hemoglobin.

3.Clincal significance داء السيلان

-Genitourinary tract infections: in males, a yellow , purulent urethral discharge & painful urination , in females, infection occur in endocervix & extends to the urethra & vagina , greenish-yellow cervical discharge , often accompanied by intermenstrual bleeding [34].

-Rectal infection: constipation painful defecation & purulent discharge[35].

-Pharyngitis: purulent pharyngeal exudate & may a mild viral or streptococcal sore throat [36].

-Ophthalmia neonatorum : is infection of the conjunctival sac acquired by newborns [37].

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[29] During passage of the baby
[30] Enhance attachment of organism to host cell surface & antigenic & virulence factors
[31] Bactericidal antibodies in normal human serum are IgM directed against LOS antigens in the cell surface
[32] Can express up to 11 different Opa protein but generally only one or few are expressed
[33] The uterus , rectum , cervix, pharynx , conjunctiva
[34] May progress to the uterus causes salpingitis “inflammation of fallopian tubes” pelvic inflammatory disease , fibrosis , infertility from tube scarring
[35] Prevalent in men who have sex with men
[36] Oral-genital contact infections

-Disseminated infection: (septic arthritis) multiply in the bloodstream , causes fever painful purulent arthritis & small , single , scattered pustules on the skin [38].

4.Laboratory identification

-Growth condition for culture: require enhanced CO2 , utilizes glucose as a carbon & energy source but not maltose , lactose , or sucrose.

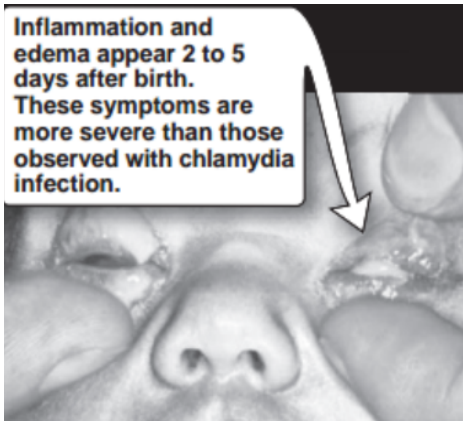
-Selective media: on Thayer Martin agar.

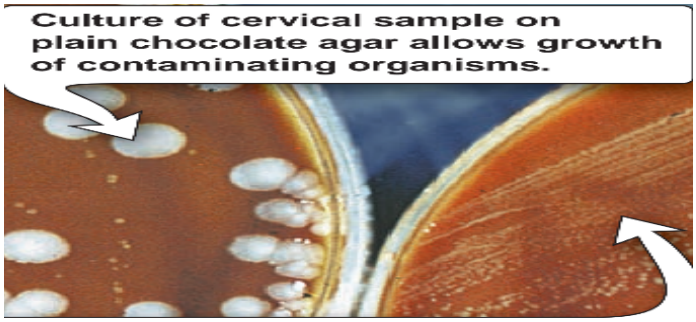
5.Treatment & prevention:

-Treatment for uncomplicated gonorrhea [39]→ Ceftriaxone [40] , Tetracycline such as Doxycycline is added when Chlamydia is suspected co-pathogen.

-Treatment for ophthalmia neonatorum → a single dose of Ceftriaxone is given systemically neonatal prophylaxis , Erythromycin is instilled into newborns to eradicate both N. gonorrhoeae and Chlamydia trachomatis.

-Prevention no vaccine or preventive drug is available , newborns whose at risk for infection are treated with prophylactically with erythromycin.





Culture on Thayer-Martin chocolate agar medium (containing vancomycin colistin, trimethoprim, and nystatin) allows selective growth of *Neisseria*.

II.Neisseria Meningitidis

1.Structure:

- Nonmotile , gram negative diplococcus , kidney shape , piliated aerobic , pyogenic , encapsulated , antiphagocytic , oxidase positive.

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[37] During passage through the birth canals of infected mother if untreated may lead to blindness , also given a systemic dose of Ceftriaxone prophylactically

[38] Base becomes red due to dilation of capillaries

[39] Of the urethra , endocervix , or rectum

[40] Dose of Azithromycin used in persons with Cephalosporin allergy

-Serogroups: A , B , C, W-135, Y.

-Serotypes: expresses PorA& PorB type porins.

2.Epidemiology:

- Transmission occurs through inhalation of respiratory droplets from carrier or patient in the early stages of the disease also contact with carrier.

3.Pathogenesis:

- Capsule aid in the maintenance of infection , LOS released during autolysis & outer membrane vesicles , the toxic effects found in disseminated[41] , make an IgA protease that cleaves IgA.

4.Clinical significance:

التهاب السحايا هو التهاب في الاغشية التي تحيط الدماغ

-Meningitis: bacteria penetrate the barrier & enter bloodstream then rapidly multiple causing meningococcemia [42] if enter blood brain barrier infects the meninges induce an acute inflammatory response , purulent meningitis , joint symptoms , purpuric rash , sever headache , rigid neck , vomiting , sensitivity to light.

-Septicemia: (Waterhouse-Friderichsen syndrome) life threatening may progress to acute fulminant septicemia large purple , blotchy skin hemorrhages , vomiting , diarrhea , circulatory collapse , adrenal necrosis & death in 10 to 12h in young children.

5.Laboratory identification;

-Culture on chocolate agar with increased CO2.

-Utilizes both glucose & maltose.

-In the CSF increased pressure , elevation of protein , decreased glucose ,many neutrophils , antigenic capsular substance confirms the diagnosis.

6.Treatment & Prevention:

-Treated immediately to prevent progression to fulminant septicemia which has high mortality by Penicillin G or Ampicillin intravenous[43].

-Prevent by a conjugate vaccine MCV4 [44] comprised of capsular material from serogroups A,B, C, W135 , Y is now recommended for adolescents & young adults [45].

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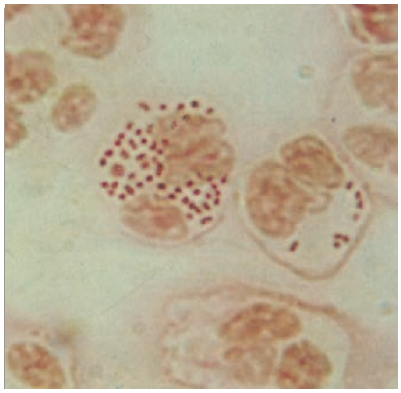
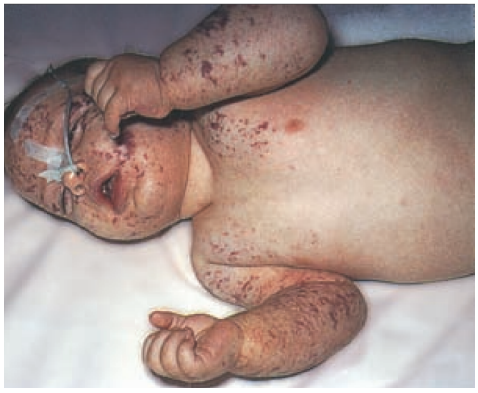
[41] Meningococcal disease
[42] Result in intravascular coagulation , circulatory collapse & potentially fatal shock
[43] If the etiology is unclear Cefotaxime or Ceftriaxone is recommended
[44] Meningococcal vaccine
[45] The polysaccharide of serogroup B does not elicit an effective immune response





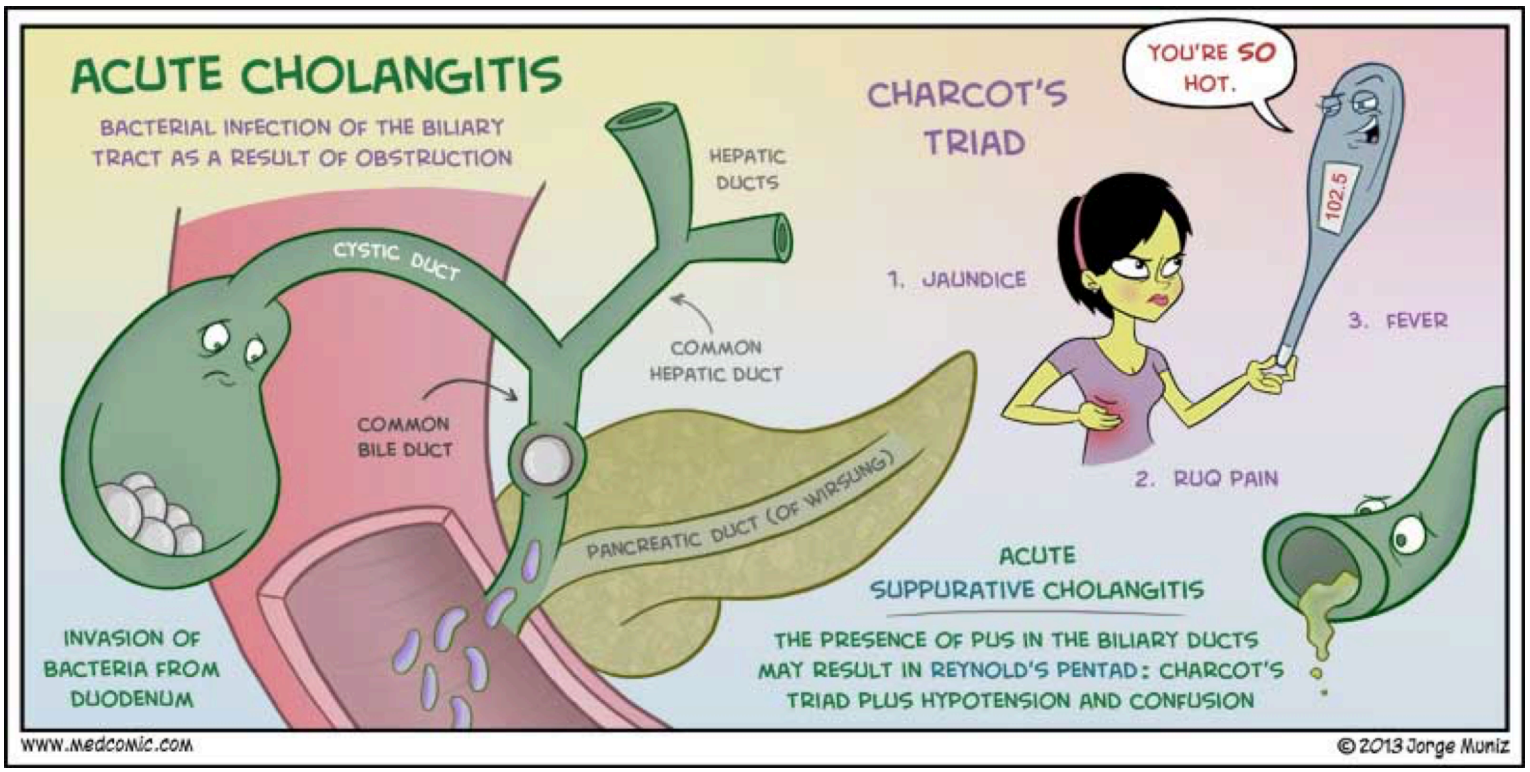
-Prophylaxis : Rifampin to treat family members to their close contact .

III.Moraxella

-Non motile , gram negative coccobacilli , found in pairs , aerobic, oxidase positive , don't ferment carbohydrates ,M. catarrhalis cause infections in respiratory, middle ear, eye, CNS, joints.

IV.Acinetobacter

-Non motile , coccobacilli , encapsulated , oxidase negative , obligately aerobic , don't ferment carbohydrates , A. baumanii is nosocomial (hospital acquired) pathogen.

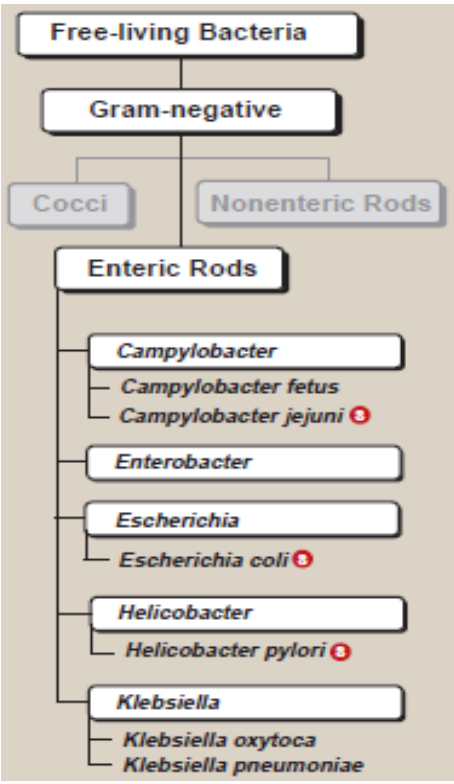


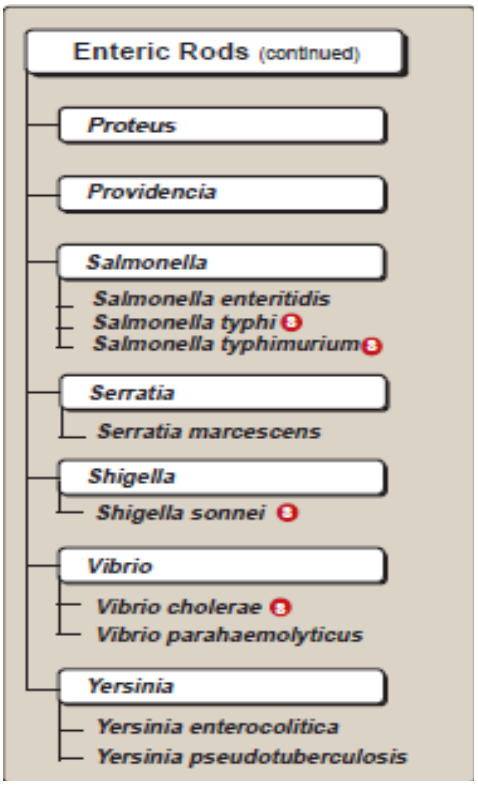
CHAPTER 12

Gastrointestinal Gram-negative

Overview:

All of the organisms covered in this chapter are routinely found in the gastrointestinal (GI) tract of humans or other animals. Many also have alternative habitats in soil or water. All are relatively hardy, but are sensitive to drying, and all grow well in the presence or absence of oxygen, being facultative anaerobes. They contain lipopolysaccharide (LPS), which is both antigenic and a potential virulence factor (endotoxin). These gram-negative rods belong to diverse taxonomic groups. They constitute only a fraction of the total microbial flora of the GI tract (most bowel organisms are either gram-positive or gram-negative anaerobes). Different enteric gram-negative rods cause diseases in the GI tract, outside the GI tract, or in both locations. Fecal contamination is frequently important in the transmission of those organisms that cause GI diseases.





ESCHERICHIA COLI:

E. coli is part of the normal flora of the colon in humans and other animals, but can be pathogenic both within and outside of the GI tract. E. coli has fimbriae or pili that are frequently important for adherence to host mucosal surfaces, and different strains of the organism may be motile or non-motile. Most strains can ferment lactose in contrast to the major intestinal pathogens, Salmonella and Shigella, which cannot ferment lactose. E. coli produces both acid and gas during fermentation of carbohydrates.

A. Structure and physiology

E. coli shares many properties with the other Enterobacteriaceae. They are all true facultative anaerobes. They all ferment glucose, and can generate energy by reducing nitrates to nitrites. They all lack cytochrome oxidase. Typing strains is based on differences in three structural antigens: O, H, and K. The O antigens are found on the polysaccharide portion of the LPS. These antigens are heat-stable, and may be shared among different Enterobacteriaceae genera. O antigens are commonly used to serologically type many of the enteric gram-negative rods. The H antigens are associated with flagella. The K antigens are most often associated with the capsule or, less commonly, with the fimbriae. Among E. coli species, there are many serologically distinct O, H, and K antigens, and specific serotypes are associated with particular diseases. For example, a serotype of E. coli possessing O157 and H7 causes a severe form of hemorrhagic colitis.

B. Clinical significance: intestinal disease

Transmission of intestinal disease is commonly by the fecal/oral route, with contaminated food and water serving as vehicles for transmission. At least five types of intestinal infections that differ in pathogenic mechanisms have been identified:

STRAIN	ABBREVIATION	SYNDROME	THERAPY[1]
Enterotoxigenic E. coli	ETEC	Watery diarrhea	Antibiotics may be useful.[2]
Enteropathogenic E. coli	EPEC	Watery diarrhea of long duration, mostly in infants, often in developing countries	Antibiotics may be useful.[2]
Enterohemorrhagic E. coli	EHEC	Bloody diarrhea; Hemorrhagic colitis and hemolytic uremic syndrome (HUS)	Avoid antibiotics because of the possible risk of potentiating HUS.
Enteroinvasive E. coli	EIEC	Bloody diarrhea	Rehydration and correction of electrolyte abnormalities.
Enteroadherent E. coli	EAEC	Persistent watery diarrhea in children and patients infected with HIV	Rehydration and correction of electrolyte abnormalities.

Characteristics of intestinal infections caused by E. coli. Fluoroquinolones are commonly used in adults for traveler's diarrhea, but are not recommended for children. 1Rehydration and correction of electrolyte abnormalities are essential for all diarrhea illnesses. 2Rifaximin is approved for the treatment of diarrhea caused by noninvasive strains of Escherichia coli in patients 12 years of age and older. Rifaximin is a nonabsorable, gastrointestinal selective, oral antibiotic.

C. Clinical significance: extraintestinal disease

The source of infection for extraintestinal disease is frequently the patient's own flora, in which the individual's own E. coli is non-pathogenic in the intestine. However, it causes disease in that individual when the organism is found, for example, in the bladder or bloodstream.

1. Urinary tract infections (UTI): E. coli is the most common cause of UTI, including cystitis and pyelonephritis. Women are particularly at risk for infection. Uncomplicated cystitis is caused by uropathogenic strains of E. coli, characterized by P fimbriae and, frequently, hemolysin, colicin V, and resistance to the bactericidal activity of serum complement. Complicated pyelonephritis occurs in settings of obstructed urinary flow, which may be caused by non-uropathogenic strains.

2. Neonatal meningitis: E. coli is a major cause of this disease occurring within the first month of life. The K1 (capsular) antigen is particularly associated with such infections.

3. Nosocomial (hospital-acquired) infections: These include sepsis/bacteremia, endotoxic shock, and pneumonia.

D. Laboratory identification

1. Intestinal disease:

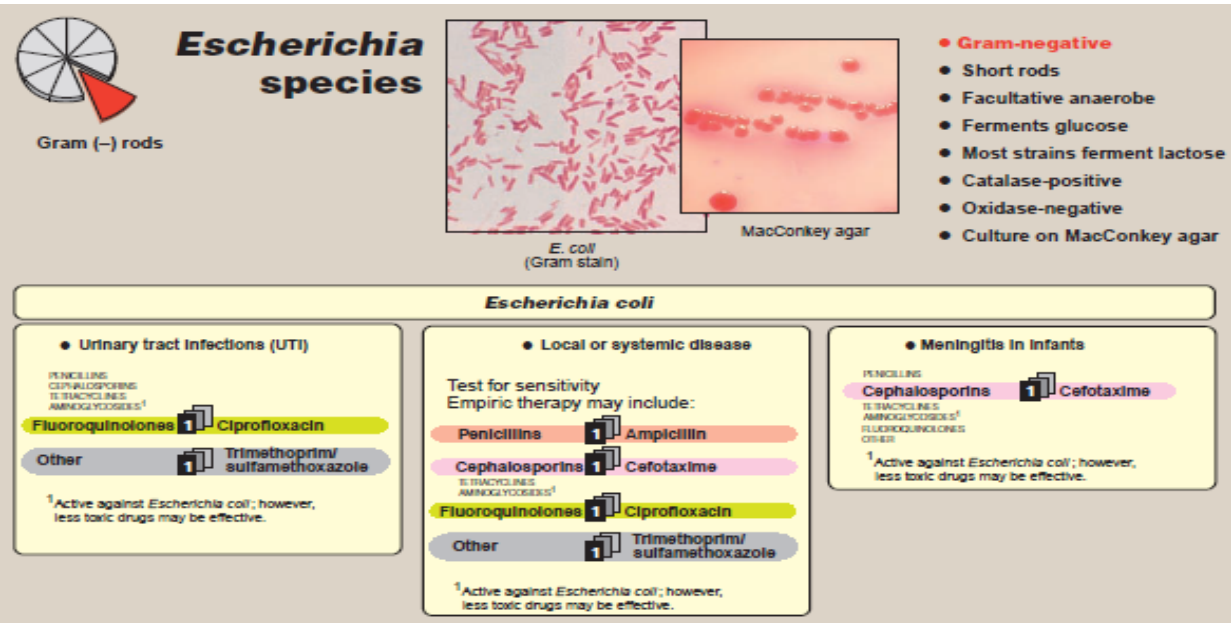
Because E. coli is normally part of the intestinal flora, detection in stool cultures of disease-causing strains is generally difficult. EIEC strains often do not ferment lactose, and may be detected on media such as MacConkey agar. EHEC, unlike most other strains of E. coli, ferment sorbitol slowly if at all, and may be detected on MacConkey sorbitol agar.

2. Extraintestinal disease:

Isolation of E. coli from normally sterile body sites is diagnostically significant. Specimens may be cultured on MacConkey agar. Strains of E. coli can be further characterized on the basis of serologic tests.

E. Treatment and prevention:

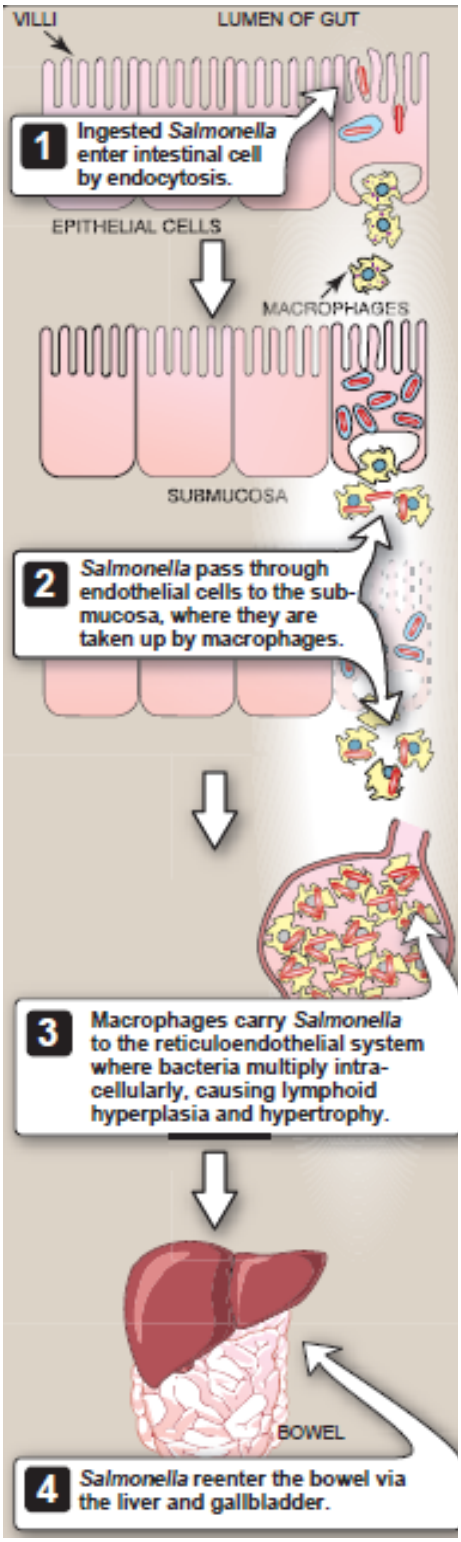
Intestinal disease can best be prevented by care in selection, preparation, and consumption of food and water. Maintenance of fluid and electrolyte balance is of primary importance in



treatment. Antibiotics may shorten duration of symptoms; however, resistance is widespread. Extraintestinal diseases require antibiotic treatment. Antibiotic sensitivity testing of isolates is necessary to determine the appropriate choice of drugs.
Summary of E. species.

SALMONELLA:

Members of the genus Salmonella can cause a variety of diseases, including gastroenteritis and enteric (typhoid) fever. Most strains of Salmonella are Lac– and produce acid and gas during fermentation of glucose. They also produce H2S from sulfur-containing amino acids.



A. Epidemiology:

Salmonella are widely distributed in nature. Serovar typhi is the exclusively human pathogen, whereas other strains are associated with animals and foods. Fecal/oral transmission occurs, and may involve chronic carriers. Pet turtles, which may be contaminated by their feed, have also been implicated as sources of infection. Young children and the elderly are particularly susceptible to Salmonella infection. Individuals in crowded institutions may also sustain Salmonella epidemics.

B. Pathogenesis:

Salmonella invade epithelial cells of the small intestine. Disease may remain localized or become systemic, sometimes with disseminated foci. The organisms are facultative, intracellular parasites that survive in phagocytic cells.

C. Clinical significance:

Salmonella infection can cause both intestinal and extraintestinal diseases.

1. Gastroenteritis (salmonellosis): This localized disease is caused primarily by serotypes enteriditis and typhimurium. It is characterized by nausea, vomiting, and diarrhea, which develop generally within 48 hours of ingesting contaminated food or water. Fever and abdominal cramping are common. In uncompromised patients, disease is generally self-limiting (48 to 72 hours), although convalescent carriage of organisms may persist for a month or more.

2. Enteric (typhoid) fever: This is a severe, life-threatening systemic illness, characterized by fever and, frequently, abdominal symptoms. It is caused primarily by serotype typhi. Nonspecific symptoms may include chills, sweats, headache, anorexia, weakness, sore throat, cough, myalgia, and either diarrhea or constipation. The incubation period varies from 5 to 21 days. Timely and appropriate antibiotic therapy reduces mortality to less than one percent, and speeds resolution of

fever. Complications can include intestinal hemorrhage and, rarely, focal infections and endocarditis. A small percentage of patients become chronic carriers.

3. Other sites of Salmonella infection: Sustained bacteremia is often associated with vascular Salmonella infections that occur when bacteria seed atherosclerotic plaque. Salmonella can also cause abdominal infections, osteomyelitis, septic arthritis, and, rarely, infections of other tissues or organs.

D. Laboratory identification:

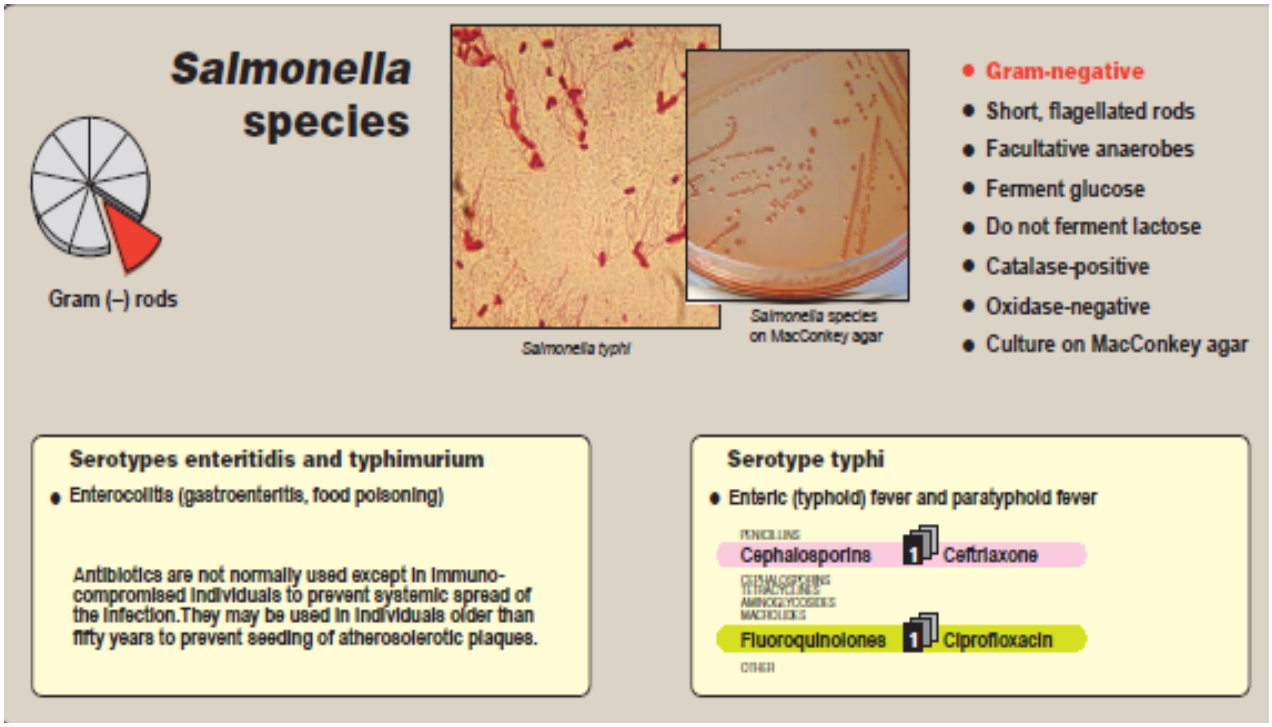
In patients with diarrhea, Salmonella can typically be isolated from stools on MacConkey agar or moderately selective media. For patients with enteric fever, appropriate specimens include blood, bone marrow, urine, stool, and tissue from typical rose spots.

E. Treatment and prevention:

For gastroenteritis in uncompromised hosts, antibiotic therapy is often not needed, and may prolong the convalescent carrier state.

For enteric fever, appropriate antibiotics include β-lactams and fluoroquinolones.

Prevention of salmonella infection is accomplished by proper sewage disposal, correct handling of food, and good personal hygiene.



CAMPYLOBACTER:

Members of the genus Campylobacter are curved, spiral, or S-shaped organisms that microscopically resemble vibrios. A single, polar flagellum provides the organism with its characteristic darting motility. Somatic, flagellar, and capsular antigens all contribute to the numerous serotypes. Most Campylobacter are microaerophilic. Members of this genus use a respiratory pathway and do not ferment carbohydrates. They infect the intestine, and can cause ulcerative, inflammatory lesions in the jejunum, ileum, or colon. Bacteremia may occur.

A. Epidemiology:

Campylobacter are widely distributed in nature as commensals of many different vertebrate species, including mammals and fowl, both wild and domestic. These serve as reservoirs of infection. Campylobacter is transmitted to humans primarily via the fecal/oral route through direct contact.

B. Pathogenesis and clinical significance:

Campylobacter may cause both intestinal and extraintestinal diseases. C. jejuni typically causes an acute enteritis in otherwise healthy individuals following an one-seven day incubation. The disease lasts days to several weeks, and, generally, is self-limiting. Symptoms may be both systemic (fever, headache, myalgia) and intestinal (abdominal cramping and diarrhea, which may or may not be bloody). C. jejuni is a cause of both traveler's diarrhea and pseudoappendicitis (symptoms simulating appendicitis without inflammation of the appendix). Bacteremia may occur, most often in infants and the elderly. Sustained bacteremia usually reflects host compromise. Complications include septic abortion, reactive arthritis, and Guillain-Barré syndrome.

C. Laboratory identification:

Campylobacter can be isolated from feces using special selective media and microaerophilic conditions. Because of their small size, these organisms are not retained by bacteriologic filters that hold back most other bacteria. Thus, filtration of the fecal suspension may enhance recovery rate. Presumptive diagnosis can be made on the basis of finding curved organisms with rapid, darting motility in a wet mount of feces.

D. Treatment and prevention:

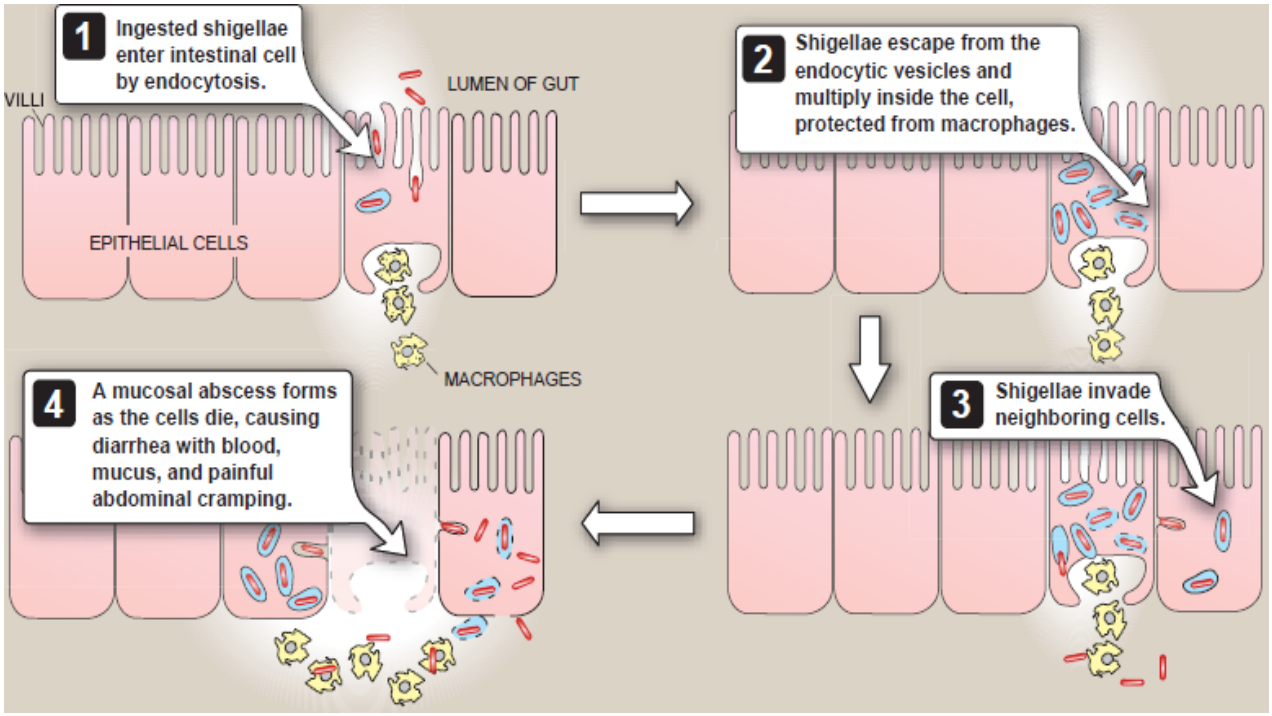
Diarrhea should be treated symptomatically with fluid and electrolyte replacement. For patients with more severe symptoms, antibiotics should be administered. For C. jejuni, ciprofloxacin is the drug of choice; other antibiotics are also effective. For C. fetus, ampicillin or third-generation cephalosporins are effective. Thorough cooking of potentially contaminated foods (for example, poultry) and pasteurization of milk and milk products is essential to prevention of campylobacteriosis. Also, surfaces used to prepare raw meat or poultry should be disinfected before using them for uncooked food, such as salads.

SHIGELLA:

Shigella species cause shigellosis (bacillary dysentery), a human intestinal disease that occurs most commonly among young children. Shigellae are nonmotile, unencapsulated, and Lac–. Most strains do not produce gas in a mixed acid fermentation of glucose.

A. Epidemiology:
Shigellae are typically spread from person to person, with contaminated stools serving as a major source of organisms. Flies and contaminated food or water can also transmit the disease. Shigellosis has a low infectious dose. Hence, secondary cases within a household are common, particularly under conditions of crowding or poor sanitation. The forty serotypes of shigella are organized into four groups (A, B, C, D) based on the serologic relatedness of their polysaccharide O antigens.

B. Pathogenesis and clinical significance:



C. Laboratory identification:
During acute illness, organisms can be cultured from stools using differential, selective Hektoen agar or other media specific for intestinal pathogens.

D. Treatment and prevention:
Antibiotics (for example, ciprofloxacin or azithromycin) can reduce the duration of illness and the period of shedding organisms, but usage is controversial because of widespread antibiotic resistance. Protection of the water and food supply, and personal hygiene are crucial for preventing shigella infections.

VIBRIO:

Members of the genus Vibrio are short, curved, rod-shaped organisms. Vibrios are closely related to the family Enterobacteriaceae. They are rapidly motile by means of a single polar flagellum. O and H antigens are both present, but only O antigens are useful in distinguishing strains of vibrios that cause epidemics. Vibrios are facultative anaerobes. The growth of many Vibrio strains either requires or is stimulated by NaCl. Pathogenic vibrios include:

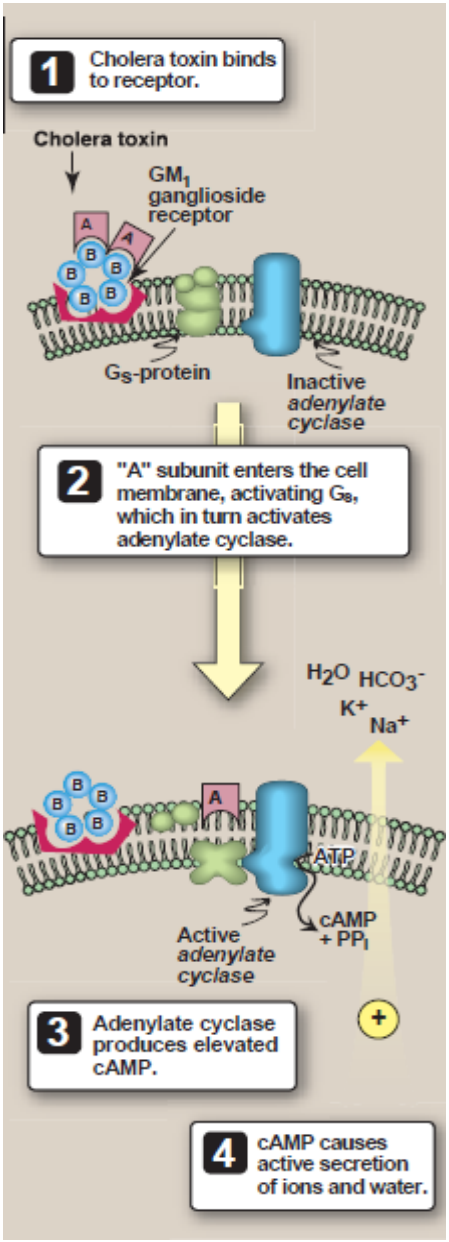
1) V. cholerae, serogroup O1 strains that are associated with epidemic cholera;
2) non-O1 V. cholerae and related strains that cause sporadic cases of choleralike and other illnesses.
3) V. parahaemolyticus and other halophilic vibrios, which cause gastroenteritis and extraintestinal infections.

A. Epidemiology:

V. cholerae is transmitted by contaminated water and food. In the acquatic environment, a number of reservoirs have been identified, including crustaceans, phytoplankton, and protozoa. Among humans, long-term carriage is considered uncommon. There are two biotypes of the species, V. cholerae: classic and El Tor. In contrast to the classic strain, the El Tor strain is distinguished by the production of hemolysins, higher carriage rates, and the ability to survive in water for longer periods. Outbreaks of both strains have been associated with raw or undercooked seafood harvested from contaminated waters.

B. Pathogenesis:

Following ingestion, V. cholerae infects the small intestine. Adhesion factor are important for colonization and virulence. Achlorhydria and/or treatments that lessen gastric acidity greatly reduce the infectious dose. The organism is noninvasive, and causes disease through the action of an enterotoxin that initiates an outpouring of fluid. Cholera toxin is a multimeric protein composed of an A and a B subunit. The B subunit binds to the GM1 ganglioside receptor of cells lining the intestine. The A subunit has two components: A2, which facilitates penetration of the cell membrane, and A1, an ADP-ribosyl transferase that ADP-ribosylates the membrane-bound Gs protein.1 Gs protein activates adenylate cyclase, which produces elevated levels of intracellular cAMP. This, in turn, causes an outflowing of ions and water to the lumen of the intestine.



C. Clinical significance:

Full-blown cholera is characterized by massive loss of fluid and electrolytes from the body. After an incubation period ranging from hours to a few days, profuse watery diarrhea begins. Untreated, death from severe dehydration causing hypovolemic shock may occur in hours to days, and the death rate may exceed fifty percent. Appropriate treatment reduces the death rate to less than one percent.

D. Laboratory identification:
V. cholerae grows on standard media such as blood and Mac-Conkey agars.
Thiosulfate–citrate–bile salts–sucrose (TCBS) medium can enhance isolation. The organism is oxidase-positive, but further biochemical testing is necessary for specific identification of V. cholerae.

E. Treatment and prevention
Replacement of fluids and electrolytes is crucial in preventing shock, and does not require bacteriologic diagnosis. Antibiotics (doxycycline) can shorten the duration of diarrhea and excretion of the organism.

F. Vibrio parahaemolyticus and other halophilic, noncholera vibrios:
These organisms are characterized by a requirement for higher than usual concentrations of NaCl, and their ability to grow in ten percent NaCl. They are common in coastal sea waters. V. parahaemolyticus is associated with outbreaks of gastrointestinal illness that result from ingestion of contaminated and inadequately cooked seafood, especially shellfish and crustaceans. The disease is selflimiting, and antibiotics do not alter the course of infection. Neither human carriers nor other mammalian reservoirs have been identified. Other halophilic, noncholera vibrios are associated with soft tissue infections and septicemia resulting either from contact of wounds with contaminated sea water or from ingestion of contaminated seafood. For soft tissue infections, prompt administration of antibiotics, such as tetracycline or cefotaxime, is important, and surgical drainage/debridement may be required. Bacteremia is associated with high mortality, especially when caused by V. vulnificus.

YERSINIA:

The genus Yersinia includes three species of medical importance: Y. enterocolitica and Y. pseudotuberculosis, both potential pathogens of the GI tract, and Y. pestis, the etiologic agent of bubonic plague. Y. enterocolitica and Y. pseudotuberculosis are both motile when grown at 25^{o}C but not at 37^{o}C. Multiple serotypes of both strains exist, and the V and W antigens are virulence factors. In contrast to most pathogenic Enterobacteriaceae, these strains of Yersinia grow well at room temperature as well as at 37^{o}C. Most strains are Lac^{-}.

A. Pathogenesis and clinical significance:
Infection occurs via ingestion of food that has become contaminated through contact with colonized domestic animals, abattoirs, or raw meat. Infection results in ulcerative lesions in the terminal ileum, necrotic lesions in Peyer patches, and enlargement of mesenteric lymph nodes. Enterocolitis caused by Yersinia is characterized by fever, abdominal pain, and diarrhea. When accompanied by right lower quadrant tenderness and leukocytosis, the symptoms are clinically indistinguishable from appendicitis. Symptoms commonly resolve in one to three weeks. Sequelae may include reactive polyarthritis and erythema nodosum. Other, less common clinical presentations include exudative pharyngitis and, in compromised patients, septicemia.

B. Laboratory identification:
Yersinia can be cultured from appropriate specimens on MacConkey or cefsulodin-irgasan-novobiocin (CIN, a medium selective for Yersinia) agars. Identification is based on

biochemical screening. In the absence of a positive culture, serologic tests for anti-Yersinia antibodies may assist in diagnosis.

C. Treatment and prevention:
Reducing infections and outbreaks rests on measures to limit potential contamination of meat, ensuring its proper handling and preparation. Antibiotic therapy (for example, with ciprofloxacin or trimethoprim-sulfamethoxazole) is essential for systemic disease (sepsis), but is of questionable value for self-limited diseases such as enterocolitis.

HELICOBACTER:

Members of the genus Helicobacter are curved or spiral organisms. They have a rapid, corkscrew motility resulting from multiple polar flagella. H. pylorus, the species of human significance, is microaerophilic, and produces urease. It causes acute gastritis and duodenal and gastric ulcers. H. pylori are unusual in their ability to colonize the stomach, where low pH normally protects against bacterial infection.

A. Pathogenesis:
Transmission of H. pylori is thought to be from person to person; the organism has not been isolated from food or water. Untreated, infections tend to be chronic, even lifelong. H. pylori colonizes gastric mucosal cells in the stomach, and metaplastic gastric epithelium in the duodenum or esophagus, but does not colonize the rest of the intestinal epithelium. The organism survives in the mucous layer that coats the epithelium, and causes chronic inflammation of the mucosa. Although the organism is noninvasive, it recruits and activates inflammatory cells. Urease released by H. pylori produces ammonia ions that neutralize stomach acid in the vicinity of the organism, favoring bacterial multiplication. Ammonia may also both cause injury and potentiate the effects of a cytotoxin produced by H. pylori.

B. Clinical significance:
Initial infection with H. pylori causes acute gastritis, sometimes with diarrhea that lasts about one week. The infection usually becomes chronic, with diffuse, superficial gastritis that may be associated with epigastric discomfort. Both duodenal ulcers and gastric ulcers are closely correlated with infection by H. pylori. H. pylori infection appears to be a risk factor for development of gastric carcinoma and gastric B-cell lymphoma [mucosaassociated lymphoid tumors (MALTomas)].

C. Laboratory identification:
Noninvasive diagnostic tests include serologic tests (ELISA for serum antibodies to H. pylori) and breath tests for urease.
Invasive tests involve gastric biopsy specimens obtained by endoscopy. H. pylori can be detected in such specimens histologically, by culture, or by a test for urease.

D. Treatment and prevention:
Elimination of H. pylori requires combination therapy with two or more antibiotics. Although H. pylori is innately sensitive to many antibiotics, resistance readily develops. A typical regimen includes amoxicillin plus clarithromycin plus a proton pump inhibitor, such as omeprazole.

OTHER ENTEROBACTERIACEAE:

Other genera of Enterobacteriaceae, such as Klebsiella, Enterobacter, Proteus, and Serratia, which can be found as normal inhabitants of the large intestine, include organisms that are primarily opportunistic and often nosocomial pathogens. Widespread antibiotic resistance among these organisms necessitates sensitivity testing to determine the appropriate antibiotic treatment.

A. Enterobacter:

Enterobacter species are motile and Lac+. They rarely cause primary disease in humans, but frequently colonize hospitalized patients, especially in association with antibiotic treatment, indwelling catheters, or invasive procedures. These organisms may infect burns, wounds, and the respiratory (causing pneumonia), or urinary tracts.

B. Klebsiella:

Klebsiellae are large, nonmotile bacilli that possess a luxurious capsule. They are Lac+. K. pneumoniae and K. oxytoca cause necrotizing lobar pneumonia in individuals compromised by alcoholism, diabetes, or chronic obstructive pulmonary disease. K. pneumoniae also causes urinary tract infections and bacteremia, particularly in hospitalized patients.

C. Serratia:

Serratia are motile and ferment lactose slowly, if at all. The species of Serratia that most frequently causes human infection is S. marcescens. Serratia can cause extraintestinal infections such as those of the lower respiratory and urinary tracts, especially among hospitalized patients.

D. Proteus, Providencia, and Morganella:

Members of these genera are agents of urinary tract and other extraintestinal infections. Proteus species are relatively common causes of uncomplicated as well as nosocomial UTIs. Other extraintestinal infections, such as wound infections, pneumonias, and septicemias, are associated with compromised patients. Proteus organisms produce urease, which catalyzes the hydrolysis of urea to ammonia. The resulting alkaline environment promotes the precipitation of struvite stones containing insoluble phosphates of magnesium and phosphate.

CHAPTER 13

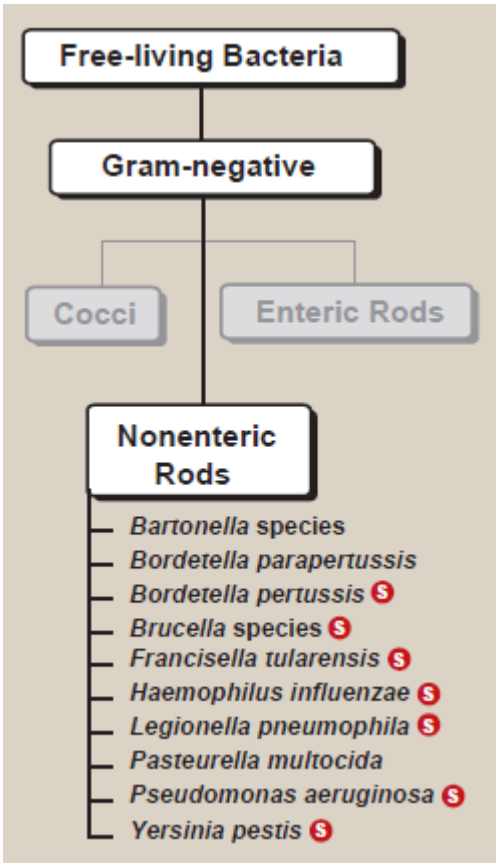
Other Gram-Negative Rods

OVERVIEW:

Although not part of a closely related family, the organisms covered in this chapter do share two significant features of structure and physiology. First, they all have a gram-negative cell envelope and, therefore, contain lipopolysaccharide (LPS), which is a virulence factor. Second, they grow in the presence of oxygen and, therefore, cause infections at sites where oxygen tension is high. It is helpful to consider these organisms as follows:

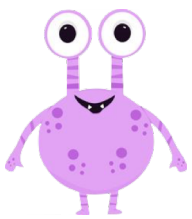
1) Those that are primarily or exclusively pathogens of the human respiratory tract.
2) Those that can infect a wide variety of tissues and whose virulence is potentiated by certain immune compromise.
3) Those that are primarily pathogens of animals.

Although Yersinia pestis is a member of the family Enterobacteriaceae, it is included in this chapter because it is a nongastrointestinal, gram-negative rod. Bartonella, another unusual gram-negative rod that is responsible for trench fever and cat scratch disease, is also described here.



HAEMOPHILUS:

Cells of Haemophilus influenzae—the major human pathogen of this genus—are pleomorphic, ranging from coccobacilli to long, slender filaments. H. influenzae may produce a capsule or may be unencapsulated. The capsule is an important virulence factor. Serious, invasive H.influenzae disease is associated particularly with capsular type b (Hib), which is composed of polyribose phosphate. Hib is especially important as a pathogen of young children, although it can cause disease in individuals of all age groups. Nontypeable (unencapsulated) strains may also cause serious disease, and are a significant cause of pneumonia among the elderly and individuals with chronic lung disease.



A. Epidemiology:

H. influenzae is a normal component of the upper respiratory tract flora in humans, and may also colonize the conjunctiva and genital tract. Humans are the only natural hosts, and colonization begins shortly after birth, with unencapsulated strains and capsular type b being carried most frequently. H. influenzae illnesses are usually sporadic in occurrence.

B. Pathogenesis:

H. influenzae is transmitted by respiratory droplets. IgA protease produced by the organism degrades secretory IgA, facilitating colonization of the upper respiratory tract mucosa. From this site, H. influenzae can enter the bloodstream and disseminate to distant sites. Diseases caused by H. influenzae, therefore, fall into two categories. First, disorders such as otitis media, sinusitis, epiglottitis, and bronchopneumonia result from contiguous spread of the organism from its site of colonization in the respiratory tract. Second, disorders such as meningitis, septic arthritis, and cellulitis result from invasion of the bloodstream, followed by localization of H. influenzae in these and other areas of the body.

C. Clinical significance:

H. influenzae has been a leading cause of bacterial meningitis, primarily in infants and very young children, frequently in conjunction with an episode of otitis media. A vaccine against H. influenzae type b, administered to infants, has dramatically decreased the frequency of such infections. Clinically, H. influenzae meningitis is indistinguishable from other purulent meningitides, and may be gradual in onset or fulminant (sudden onset with great severity).

D. Laboratory identification:

A definitive diagnosis generally requires identification of the organism; for example, by culture on chocolate agar. Isolation from normally sterile sites and fluids such as blood, cerebrospinal fluid (CSF), or synovial fluid, is significant, whereas isolation from pharyngeal cultures is inconclusive. Rapid diagnosis is crucial because of the potentially fulminant course of type b infections. In cases of meningitis, Gram staining of CSF commonly reveals pleomorphic, gram-negative coccobacilli. Type b capsule may be demonstrated directly in CSF, either by the capsular swelling (quellung) reaction or by immunofluorescent staining. Capsular antigen may be detected in CSF or other body fluids using immunologic tests, such as latex agglutination, countercurrent immunoelectrophoresis, and radioimmunoassay.

E. Treatment:

When invasive H. influenzae is suspected, a suitable antibiotic (for example, a third-generation cephalosporin such as ceftriaxone or cefotaxime) should be started as soon as appropriate specimens have been taken for culture. Antibiotic sensitivity testing is necessary

because of emergence of strains resistant to antibiotics commonly used to treat H. influenzae (for example, strains with β-lactamase-mediated ampicillin resistance). Sinusitis, otitis media, and other upper respiratory tract infections are treated with trimethoprim-sulfamethoxazole or ampicillin plus clavulanate.

F. Prevention:

Active immunization against Hib is effective in preventing invasive disease, and also reduces respiratory carriage of Hib. The current vaccine, generally given to children younger than two years, consists of Hib polyribose phosphate (PRP) capsular carbohydrate conjugated to a carrier protein. Rifampin is given prophylactically to individuals in close contact with a patient infected with H. influenzae—particularly those patients with invasive disease (for example, H. influenzae meningitis).

BORDETELLA:

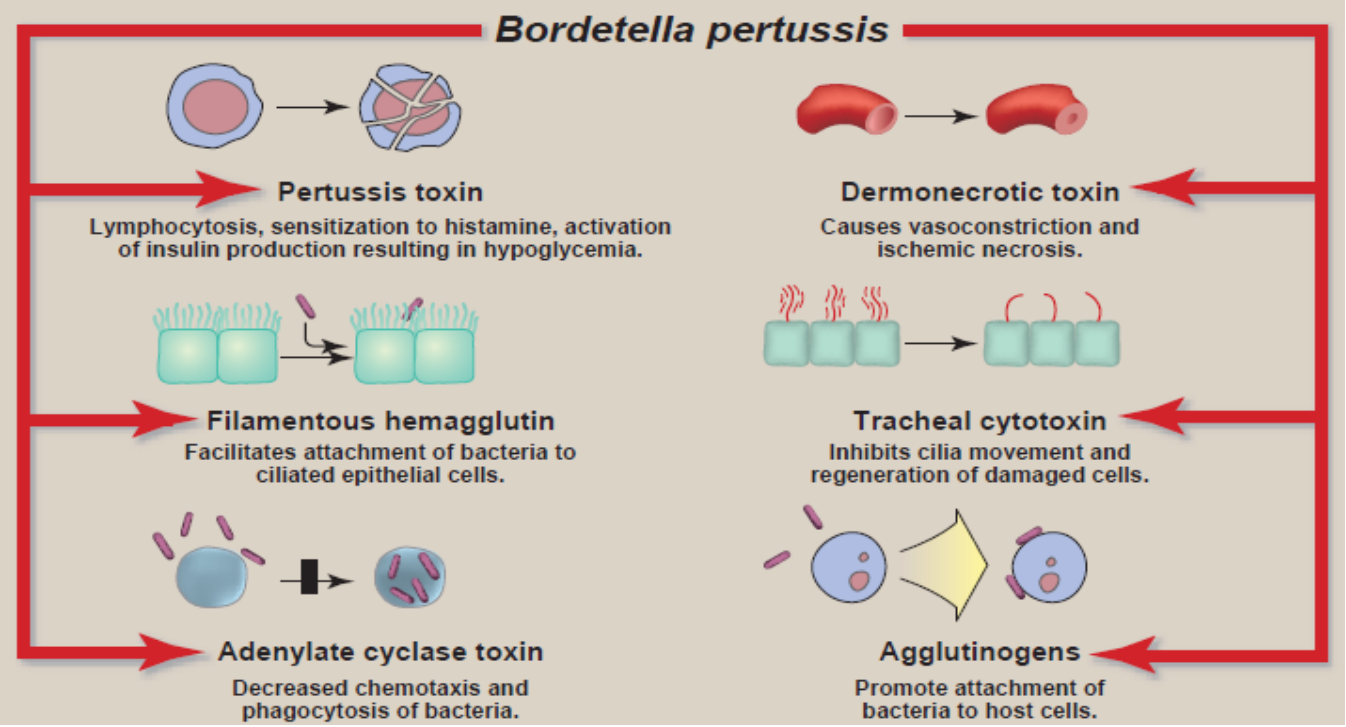
Bordetella pertussis and B. parapertussis are the human pathogens of this genus. The former causes the disease pertussis, and the latter causes a mild pertussis-like illness. Whooping cough is a highly contagious disease and a significant cause of morbidity and mortality worldwide. Members of the genus Bordetella are aerobic. They are small, encapsulated coccobacilli that grow singly or in pairs. They can be serotyped on the basis of cell-surface molecules including adhesins and fimbriae.

A. Epidemiology:

The major mode of transmission of Bordetella is via droplets spread by coughing, but the organism survives only briefly outside the human respiratory tract. The incidence of whooping cough among different age-groups can vary substantially, depending on whether active immunization of young children is widespread in the community. In the absence of an immunization program, disease is most common among young children (ages 1 to 5 years).

B. Pathogenesis:

B. pertussis binds to ciliated epithelium in the upper respiratory tract. There, the bacteria produce a variety of toxins and other virulence factors that interfere with ciliary activity, eventually causing death of these cells.



C. Clinical significance:

The incubation period for pertussis generally ranges from one to three weeks. The disease can be divided into two phases: catarrhal and paroxysmal.

1. Catarrhal phase: This phase begins with relatively nonspecific symptoms such as rhinorrhea, mild conjunctival infection (hyperemia, or bloodshot), malaise, and/or mild fever, and then progresses to include a dry, nonproductive cough. Patients in this phase of disease are highly contagious.

2. Paroxysmal phase: With worsening of the cough, the paroxysmal phase begins. The term whooping cough derives from the paroxysms of coughing followed by a "whoop" as the patient inspires rapidly. Large amounts of mucus may be produced. Paroxysms may cause cyanosis and/or end with vomiting. Pertussis typically causes leukocytosis that can be quite striking as the total white blood cell count sometimes exceeds 50,000 cells/μL (normal range = 4500–11,000 white blood cells/μL), with a striking predominance of lymphocytes. Following the paroxysmal phase, convalescence requires at least an additional three to four weeks. During this period, secondary complications such as infections (for example, otitis media and pneumonia) and CNS dysfunction (for example, encephalopathy or seizures) may occur. Disease is generally most severe in infants.

D. Laboratory identification:

Presumptive diagnosis may be made on clinical grounds once the paroxysmal phase of classic pertussis begins. Pertussis may be suspected in an individual who has onset of catarrhal symptoms within one to three weeks of exposure to a diagnosed case of pertussis. Culture of B. pertussis from the nasopharynx of a symptomatic patient supports the diagnosis. The organism produces pinpoint colonies in three to six days on selective agar medium, for

example, one that contains blood and charcoal, which serves to absorb and/or neutralize inhibitory substances, and is supplemented with antibiotics to inhibit growth of normal flora. More rapid diagnosis may be accomplished using a direct fluorescent antibody (DFA) test to detect B. pertussis in smears of nasopharyngeal specimens.

E. Treatment:

Erythromycin is the drug of choice for infections with B. pertussis, both as chemotherapy (where it reduces both the duration and severity of disease), and as chemoprophylaxis for household contacts. For erythromycin treatment failures, trimethoprim-sulfamethoxazole is an alternative choice.

F. Prevention:

Pertussis vaccine is available that has had a significant effect on lowering the incidence of whooping cough. It contains proteins purified from B. pertussis, and is formulated in combination with diphtheria and tetanus toxoids. To protect infants who are at greatest risk of life-threatening B. pertussis disease, immunization is generally initiated when the infant is two months old. The availability of an effective vaccine led to a dramatic decrease in the incidence of the disease in the United States.

LEGIONELLA:

Legionellaceae are facultative intracellular parasites that cause primarily respiratory tract infections. In nature, Legionella cells are unencapsulated, relatively slender rods; however, in clinical material, they appear coccobacillary in shape. Members of the Legionellaceae family are aerobic and fastidious, with a particular requirement for L-cysteine.

A. Epidemiology:

The Legionellaceae family includes 34 species whose normal habitat is soil and water, including in cooling towers and water distribution systems. About 85 to 90 percent of human disease is caused by a single species, Legionella pneumophila. Most infections result from inhalation of aerosolized organisms but, occasionally, may follow other exposures. Both sporadic cases and localized outbreaks may occur. The organism is chlorine tolerant and thus survives water treatment procedures.

B. Pathogenesis:

The organism gains entry to the upper respiratory tract by aspiration of water containing the organism, or by inhalation of a contaminated aerosol. Failure to clear the organisms permits them to reach the lungs. Alveolar macrophages in the lung bed normally constitute an important line of defense for clearing invading organisms. Although the macrophages do phagocytose L.pneumophila, the resulting phagosome fails to fuse with a lysosome. Instead, the organism multiply within the protected environment of the phagosome until the cell ruptures, releasing a new crop of bacteria.

C. Clinical significance:

Legionellaceae primarily cause respiratory tract infections. There are two distinctly different presentations: Legionnaires' disease and Pontiac fever. The factors that determine which presentation will occur are not understood, although the condition of the host likely plays a role.

1. Legionnaires' disease (LD): This is an atypical, acute lobar pneumonia with multisystem symptoms. It may occur sporadically or in outbreaks (for example, nosocomial outbreaks have occurred). LD typically develops in only one to five percent of individuals exposed to a common source. Legionellae are estimated to cause one to five percent of the cases of community-acquired pneumonias in adults. The case fatality rate for LD ranges from five to thirty percent, a high rate that may reflect the fact that many LD patients have additional contributing factors, such as pulmonary disease or immunocompromise factors. Symptoms develop after an incubation period ranging from 2 to 10 days. Early symptoms may be relatively nonspecific: fever, malaise, myalgia, anorexia, and/or headache. The severity and range of symptoms associated with LD vary substantially. A cough that is only slightly productive then appears, sometimes with respiratory compromise. Diarrhea (watery rather than bloody stools) occurs in 25 to 50 percent of cases. Nausea, vomiting, and neurologic symptoms may also occur.

2. Pontiac fever: This is an influenza-like illness that characteristically infects otherwise healthy individuals. The attack rate among those exposed to a common source is typically ninety percent or more. Recovery is usually complete within one week. No specific therapy is required.

D. Laboratory identification:

LD cannot be diagnosed unambiguously on the basis of clinical presentation or radiologic appearance of lungs. Although the organism can be Gram stained, the Gimenez stain is more useful for visualization. The definitive method of diagnosis involves the culturing of Legionella from respiratory secretions, using buffered (pH 6.9) charcoal yeast extract enriched with L-cysteine, iron, and α-ketoglutarate. Visible colonies form in three to five days. A urinary antigen test using an enzyme immunoassay is available and has several advantages over culture. For example, the test positivity can persist for days even during administration of antibiotic therapy making it useful in patients who receive empiric anti-Legionella therapy. Further, the results of the urinary antigen test can be available within hours, whereas culture results require three to five days.

E. Treatment:

Macrolides, such as erythromycin or azithromycin, are the drugs of choice for Legionnaires disease. Fluoroquinolones are also effective. Pontiac fever is usually treated symptomatically, without antibiotics.

PSEUDOMONAS:

Pseudomonas aeruginosa, the primary human pathogen in the genus Pseudomonas, is widely distributed in nature. Although it may colonize healthy humans without causing disease, it is also a significant opportunistic pathogen and a major cause of nosocomial (hospital-acquired) infections. P. aeruginosa is regularly a cause of nosocomial pneumonia, nosocomial urinary tract infections, surgical site infections, infections of severe burns, and infections of patients undergoing either chemotherapy for neoplastic disease or antibiotic therapy. P. aeruginosa is motile, encapsulated, and aerobic or facultative. Nutritional requirements are minimal, and the organism can grow on a wide variety of organic substrates. In fact, P. aeruginosa can even grow in laboratory water baths, hot tubs, wet IV tubing, and other water-containing vessels. This explains why the organism is responsible for so many nosocomial infections.

A. Pathogenesis:

P. aeruginosa disease begins with attachment to and colonization of host tissue. Pili on the bacteria mediate adherence, and a mucoid capsule which reduces the effectiveness of normal clearance mechanism. Host tissue damage facilitates adherence and colonization. P. aeruginosa produces numerous toxins and extracellular products that promote local invasion and dissemination of the organism.

B. Clinical significance:

P. aeruginosa causes both localized and systemic illness. Virtually any tissue or organ system may be affected. Individuals most at risk include those with impaired immune defenses.

1. Localized infections: These may occur in the eye (keratitis and endophthalmitis, following trauma), ear (external otitis or swimmer's ear; invasive and necrotizing otitis externa, particularly in elderly diabetic patients or trauma patients), skin (wound sepsis, pustular rashes occurring in epidemics associated with use of contaminated whirlpools, hot tubs, and swimming pools), urinary tract (particularly in hospitalized patients who have been subjected to catheterization, instrumentation, surgery, or renal transplantation), respiratory tract (pneumonia in individuals with chronic lung disease, congestive heart failure, or cystic fibrosis, and particularly in patients who have been intubated or are on ventilators), gastrointestinal tract (infections range from relatively mild diarrheal illness in children to severe, necrotizing enterocolitis in infants and neutropenic cancer patients), and the central nervous system (CNS; meningitis and brain abscesses, particularly in association with trauma, surgery, or tumors of the head or neck). Localized infections have the potential to lead to disseminated infection.

2. Systemic infections: Infections reflecting systemic spread of the organism include bacteremia (most common in patients whose immune system have been compromised), secondary pneumonia, bone and joint infections (in IV drug users and patients with urinary tract or pelvic infections), endocarditis (in IV drug users and patients with prosthetic heart valves), CNS (mainly when the meninges are breached), and skin/soft tissue infections.

C. Laboratory identification:

P. aeruginosa can be isolated by plating on a variety of media, both nonselective (for example, blood agar) and moderately selective (for example, MacConkey agar). Identification is based on the results of a battery of biochemical and other diagnostic tests. Serologic typing is used in the investigation of clusters of cases, which may stem from exposure to a common source.

D. Treatment and Prevention:

Specific therapy varies with the clinical presentation and the antibiotic sensitivity pattern of the isolate. It is difficult to find antibiotics effective against P. aeruginosa, because of its rapid development of resistance mutations and its own innate mechanisms of antibiotic resistance. Pseudomonas infections typically occur in patients with impaired defenses. Therefore, aggressive antimicrobial therapy (often a combination of two bactericidal antibiotics, such as an aminoglycoside, an antipseudomonal β-lactam, or a quinolone) is generally required.

VI. BRUCELLA

Members of the genus Brucella are primarily pathogens of animals. Thus, brucellosis (undulant fever) is a zoonosis (a disease of animals that may be transmitted to humans under natural conditions).
Different species of Brucella:
Brucella abortus (cattle),Brucella melitensis(goats and sheep), Brucella suis (swine).
Brucella canis (dogs),and Brucella ovis (sheep).
The brucellae are aerobic, facultatively intracellular parasite,that can survive and multiply within host phagocytes. Cells of the genus Brucella are unencapsulated, small coccobacilli arranged singly or in pairs (see Figure 13.15).

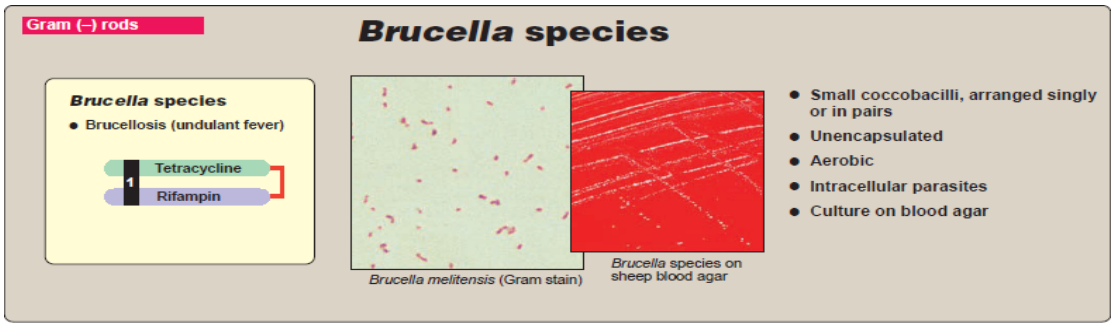


Figure 13.15
Summary of *Brucella* disease. 1 Indicates first-line drugs.

A.Epidemiology:

is a chronic, lifelong infection in animals. Organisms localize in reproductive organs (male and female) and are shed in large numbers in milk, urine, the placenta and other tissues discharged during delivery or spontaneous abortion. Transmission to humans either direct contact with infected animal tissue or ingestion of unpasteurized milk or milk products (Figure 13.14).

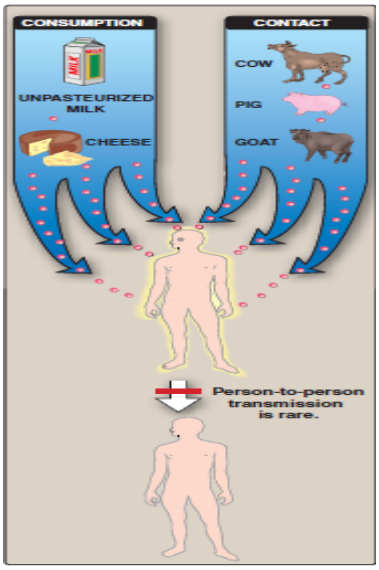


Figure 13.14
Transmission of *Brucella*.

B. Pathogenesis:
Brucellae typically enter the body through cuts and abrasions in the skin or through the gastrointestinal (GI) tract. Drugs that decrease gastric acidity may increase the likelihood of transmission via the GI route.

C. Clinical significance:
The incubation period for Brucella infections ranges from 5 days to several months. Symptoms are nonspecific and flulike (malaise, fever, sweats, anorexia, GI symptoms, headache, and back pains), depression. Manifestations of brucellosis may involve any of a variety of organ systems, including the GI tract and the skeletal, neurologic, cardiovascular, and pulmonary systems.

D. Laboratory identification:
A detailed history is often crucial because of the nonspecific symptoms. The organism can be cultured from blood and other body fluids, or from tissue specimens, but isolation of the organism is difficult and time consuming.

E. Treatment:
Combination therapy involving doxycycline and rifampin is generally recommended for brucellosis. Prolonged treatment (for example, 6 weeks) is generally necessary to prevent relapse and reduce the incidence of complications.

VII. FRANCISELLA TULARENSIS

Figure 13.16
Electron micrograph showing the pleomorphic cells of *Francisella tularenis*.

Francisella tularensis is primarily a pathogen of animals. Thus, tularemia (also known as rabbit fever and deerfly fever) is a zoonosis. The cells are small, pleomorphic coccobacilli that possess a polysaccharide capsule, which, although nontoxic, is a virulence factor (Figure 13.16). The organisms are facultative anaerobes.

A. Epidemiology:
The host range of F. tularensis is broad, and includes wild and domestic mammals, birds, and house pets. A number of biting or blood-sucking arthropods serve as vectors. Transmission is, thus, by contact with infected animal tissues, contaminated water, or an arthropod bite. Tularemia is an occupational risk for veterinarians, hunters and trappers, domestic livestock workers, and meat handlers. During the winter months, a smaller peak incidence occurs, which reflects exposure of hunters to infected animal carcasses. Infection is also more common in males, because they have a greater exposure risk. There is no person-to-person transmission.

B-Pathogenesis:
In cases involving cutaneous inoculation, the organism multiplies locally for 3 to 5 days. It typically produces a papule that ulcerates after several days and may persist for weeks or longer. Organisms spread from the local lesion to the regional lymph nodes ,the organisms spread via the lymphatic system to various organs and tissues, including skin, lungs, liver, spleen, kidneys, and CNS.

C. Clinical significance:
Tularemia varies in severity from mild to fulminant and fatal. Onset of symptoms is usually abrupt. The most common symptoms are flulike (chills, fever, headache, malaise, anorexia, and fatigue), although respiratory and GI symptoms may also occur.

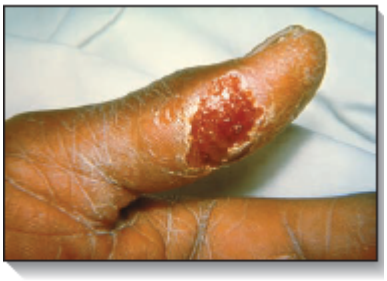


Figure 13.17
Thumb with skin ulcer of tularemia.

Ulceroglandular tularemia: The most common presentation of tularemia is ulceroglandular (Figure 13.17). Ulcers may result from contact with contaminated animal products (typically on the hands and/or forearms) or from insect bites (commonly on the trunk and/or lower extremities). Lymphadenopathy is characteristic.

D. Laboratory identification Clinical presentation and history consistent with possible exposure is of primary importance in diagnosis. The organism may be cultured from ulcer scrapings, lymph node biopsies, gastric washings, and
sputum but rarely from blood.

E. Treatment The drug of choice for treatment of the forms of tularemia discussed above is streptomycin or gentamicin plus a tetracycline (Figure 13.18).

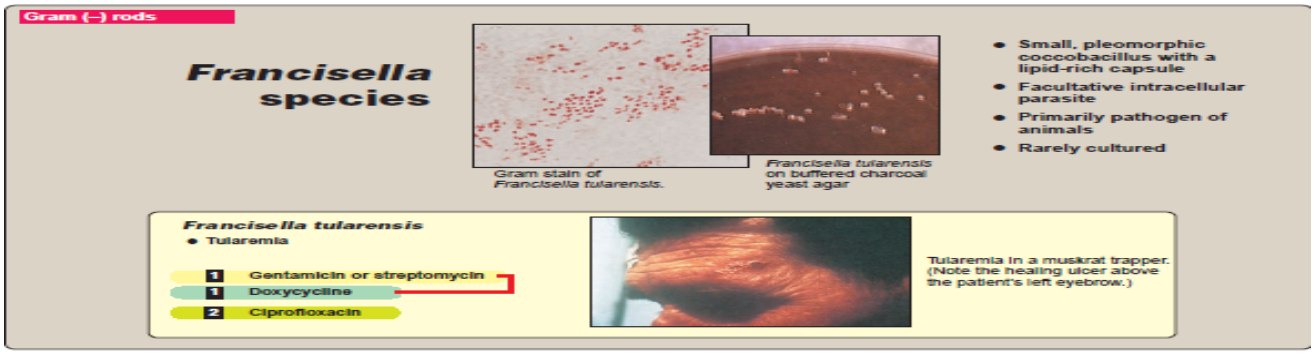


Figure 13.18
Summary of *Francisella* species. 1 Indicates first-line drugs; 2 indicates alternative drugs.

VIII. YERSINIA PESTIS

The genus Yersinia is a member of the family Enterobacteriaceae. The most clinically notorious member of this genus is Yersinia pestis, which causes plague .Y. pestis is a small rod that stains bipolarly (see Figure 13.21). Y. pestis produces a variety of plasmid- encoded virulence factors that are immunosuppressive or antiphagocytic.

Figure 13.21
Summary of *Yersinia pestis* disease. 1 Indicates first-line drugs. CIN = cefsulodin-Irgasan-novobiocin.

A. Epidemiology

Plague is predominantly a zoonosis with worldwide distribution. In the United States, the Southwest has been a primary focus of
Y. pestis infection. Plague is characteristically transmitted
by fleas, which serve to maintain the infection within the animal
reservoir. Humans are generally accidental and dead-end hosts.
Plague can also be transmitted by ingestion of contaminated animal tissue or via the respiratory route (pneumonic plague).

B-Pathogenesis:

Organisms are carried by the lymphatic system from the site of inoculation to regional lymph nodes, where they are ingested by phagocytes. Y. pestis multiplies in these cells. Hematogenous spread of bacteria to other organs
and tissues may occur, resulting in hemorrhagic lesions at these sites.

C.Clinical significance:

Plague may present several clinically different pictures. Most common is the bubonic/septicemic form. Pneumonic plague may result of spread to the lungs during septicemic plague or may be spread person-to-person via the respiratory route. Less common presentations plague meningitis , cutaneous plague, and pharyngitis .

1- Bubonic (septicemic) plague

The incubation period (from flea bite to development of symptoms) is generally 2 to 8 days. Onset of nonspecific symptoms, such as high fever, chills, headache, myalgia, and weakness that proceeds to prostration, is characteristically sudden. Within a short time, the characteristic, painful **buboes** develop (Figure 13.20)., typically in the groin, but they may also occur in axillae or on the neck. Blood pressure drops, potentially leading to septic shock and death.

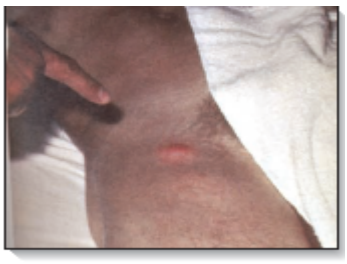


Figure 13.20
Bubo characteristic of infections due to *Yersinia pestis*.

2- Pneumonic plague

If plague bacilli reach the lungs, they cause hemorrhagic pneumonia that, if untreated, is rapidly fatal. It is also highly contagious person to person. The organisms can cause
pneumonic plague directly if inhaled.

3. Plague meningitis:
This results from hematogenous dissemination of organisms to the meninges. It may occur following inadequately treated bubonic plague or, like septicemic plague, may occur without, or prior to, development of a bubo. Organisms can be demonstrated
in the CSF.

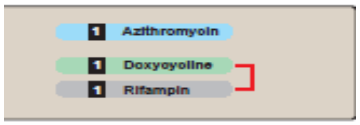


Figure 13.22
Antimicrobial agents useful in therapy of infections caused by *Bartonella* species.
1 Indicates first-line drugs.

D. Laboratory identification

Can be initiated by a gram-stained smear, and culture of an aspirate from a bubo (or from CSF or sputum in the case of meningitis or pneumonic presentations). The organism grows on both MacConkey and blood agar media, although colonies grow somewhat more slowly than those of other Enterobacteriaceae.

E. Treatment

Streptomycin is the drug of choice, but gentamicin and doxycycline
are acceptable alternatives . For plague meningitis, chloramphenicol offers good penetration into the CSF. Because of the potential for overwhelming septicemia, rapid institution of antibiotic therapy is crucial. Supportive therapy is essential for patients with signs of shock. A formalin-killed vaccine is available for those at high risk of acquiring plague.

IX. BARTONELLA

Members of the genus Bartonella (formerly, Rochalimaea), facultative,
intracellular parasites, can be cultivated on special media in the laboratory.
Two species have been implicated in human diseases.

A. Bartonella Quintana
causes trench fever, an often mild, relapsinghumans, and its vector is the human body louse. Specific diagnosis can be aided by culture of clinical materials and serologic tests. Broad-spectrum
antibiotics are effective in the treatmentof the disease (Figure 13.22).

B. Bartonella henselae
was recently shown to be associated with most cases of cat scratch disease, a syndrome that has been familiar to physicians for decades, but whose etiology had been elusive. The illness is characterized by small abscesses at the site of a cat (less
commonly, other pets) scratch or bite. This is followed by fever and localized lymphadenopathy. B. henselae is also responsible for several other types of infections such as bacillary angiomatosis seen primarily in immunocompromised patients such as those with AIDS. are successfully treated with rifampin in combination with doxycycline (see Figure 13.22).

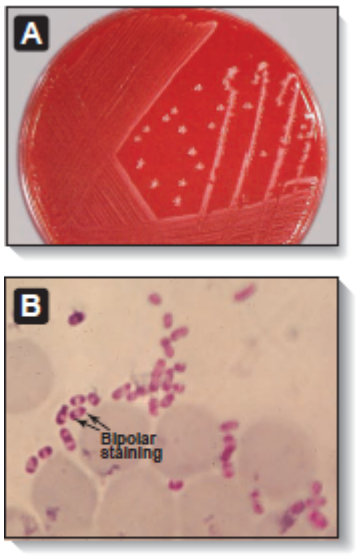


Figure 13.23
Pasteurella multocida. A. Culture on blood agar showing small, translucent

X. PASTEURELLA

Members of the genus Pasteurella primarily colonize mammals and birds.infections are considered zoonoses. The major human pathogen in this genus is Pasteurella multocida, which can cause disease or

asymptomatic infections. Pasteurellae are coccobacilli or rods that often exhibit bipolar staining, and some strains are encapsulated (Figure 13.23). Virulence factors include the organism's capsule and endotoxin. Pasteurellae are aerobes or facultative anaerobes.

A. Epidemiology

The majority of Pasteurella infections in humans are soft tissue
infections that follow an animal bite or cat scratch. A smaller fraction of human Pasteurella infections occur either following a non-bite animal exposure or in the absence of any known animal exposure.

B. Clinical significance

P. multocida infection should be suspected in cases of acute, painful cellulitis that develop within 24 hours of an animal bite or cat scratch. Soft tissue infections are characterized by the rapid onset of acute local inflammation within hours of the bite or scratch. Lesions often begin to drain within 1 to 2 days. Manifestations of P. multocida infection include cellulitis, lymphangitis; lymphadenitis, fever, and local complications, such as osteomyelitis and arthritis, which can result in extended disability.

C. Laboratory identification

Laboratory diagnosis by culturing the organism on blood agar and performing appropriate biochemical tests.

D. Treatment

For soft tissue infections, wounds should be cleansed, irrigated, and debrided. Deep-seated infections require surgical drainage and prolonged antibiotic treatment. Penicillin is the drug of choice (Figure 13.24). Fatal infections are uncommon.

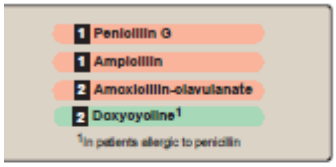
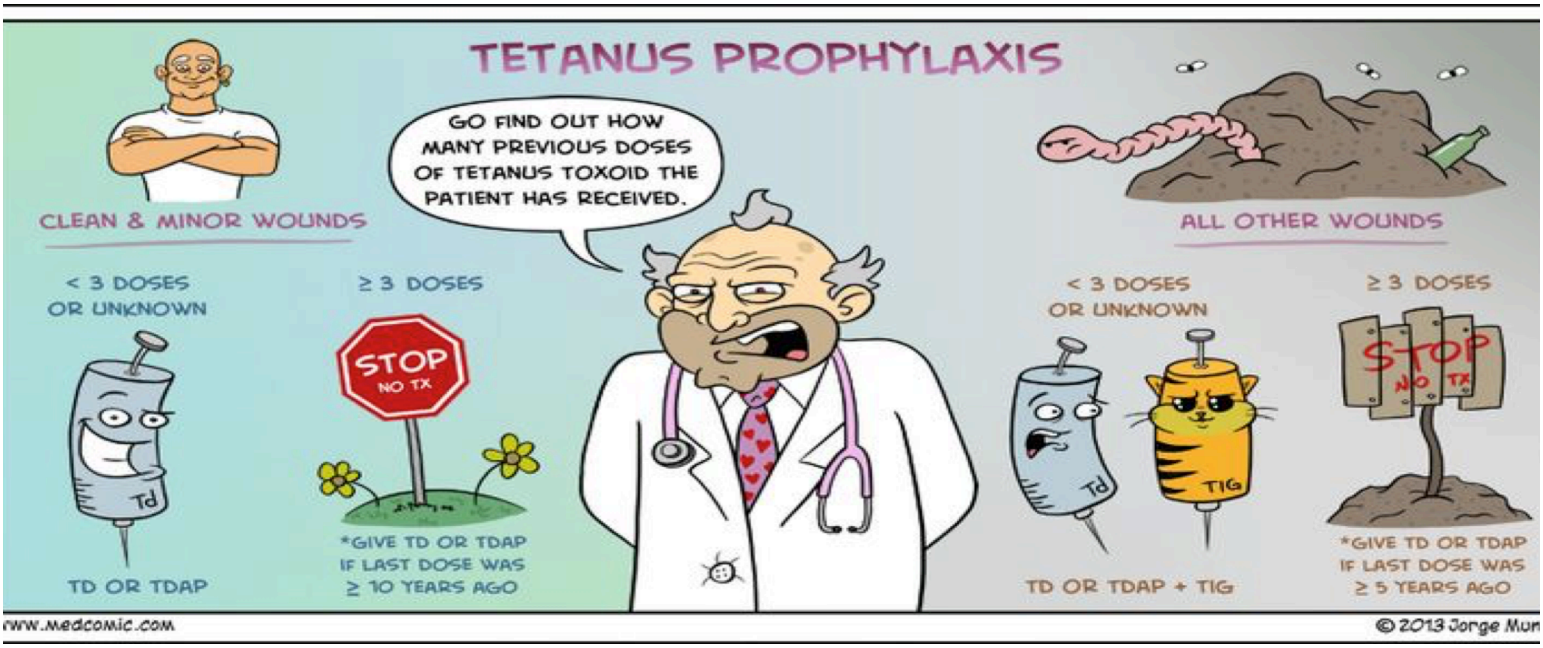


Figure 13.24
Antimicrobial agents useful in therapy of infections caused by *Pasteurella multocida*. 1 Indicates first-line drugs; 2 indicates alternative drugs.



CHAPTER 14
Clostridia and Other Anaerobic

I. OVERVIEW

The organisms discussed in this chapter are all obligate anaerobes. These microorganisms obtain energy exclusively by fermentation, and the presence of oxygen is inhibitory to their growth. The obligate anaerobic genus, Clostridium, consists of gram-positive, spore-forming rods that are associated with soft tissue and skin infections (for example, cellulitis and fasciitis), and antibiotic-associated colitis and diarrhea. These organisms also synthesize some of the most potent exotoxins known. A number of anaerobic, gram-negative rods, such as Bacteroides and related genera, are frequently involved in visceral and other abscesses. The organisms discussed in this chapter are listed in Figure 14.1.

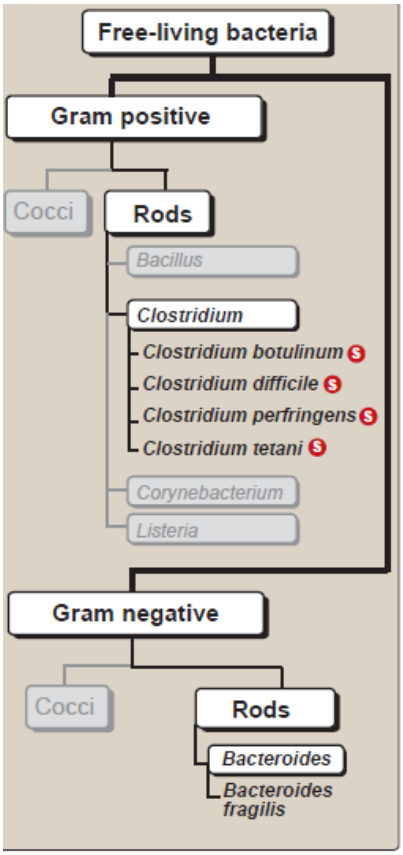


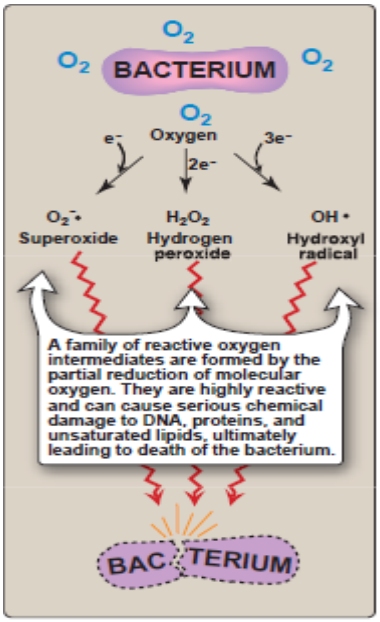
Figure 14.1

II. CLOSTRIDIA

Clostridia are the anaerobic gram-positive rods of greatest clinical importance. Other clinically important gram-positive rods are aerobic. Clinically significant species of Clostridium include Clostridium perfringens, which causes histotoxic tissue destructive) infections (myonecrosis) and food poisoning; Clostridium difficile, which causes pseudomembranous colitis associated with antibiotic use; lostridium tetani, which causes tetanus ("lockjaw"); and Clostridium botulinum, which causes botulism.

A. General features of clostridia

Clostridia are large, gram-positive, blunt-ended rods. They form endospores, and the position of the developing spore within the vegetative cell is useful in identifying the species. Most species are motile.



1. Physiology: Clostridia cannot use free oxygen as the terminal electron acceptor in energy production as do aerobic organisms. Instead, they use a variety of small organic molecules, such as pyruvate, as the final electron acceptors in the generation of energy. In the vegetative state, Clostridia are also variably inhibited or damaged by O2 (Figure 14.2).

2. Epidemiology: Clostridia, part of the intestinal flora in humans and other mammals, are found in soil, sewage, and aquatic settings,

particularly those with high organic content. A number of clostridial species produce destructive and invasive infections when introduced into tissues (for example, by a break in the skin resulting from surgery or trauma).

B. Clostridium perfringens

C. perfringens is a large, nonmotile, gram-positive, encapsulated
bacillus. It is ubiquitous in nature, with its vegetative form as part of the normal flora of the vagina and gastrointestinal (GI) tract.
When introduced into tissue, however, C. perfringens can cause anaerobic cellulitis and myonecrosis (gas gangrene). Some strains of C. perfringens also cause a common form of food poisoning.

1-Pathogenesis:

C. perfringens secretes a variety of exotoxins,
enterotoxins, and hydrolytic enzymes that facilitate the disease
process .

2. Clinical significance:

The disease processes initiated by C. perfringens result from a combination of infection and the production of exotoxins and/or enterotoxins and degradative enzymes.

a. **Myonecrosis (gas gangrene):** Clostridial spores are introduced into tissue, by contamination with infected soil, or by endogenous transfer from the intestinal tract. Severe and open wounds, such as compound fractures and other ischemia producing injuries (for example, crush injuries), are a prime predisposing condition. Fermentation of tissue carbohydrates, lipids, and amino acids yields gas, and an accumulation of gas bubbles in the subcutaneous spaces produces a crinkling sensation on palpation (crepitation), hence, the name “gas gangrene” ((Figure 14.4). Untreated clostridial myonecrosis is uniformly fatal within days of the initiation of gangrene.

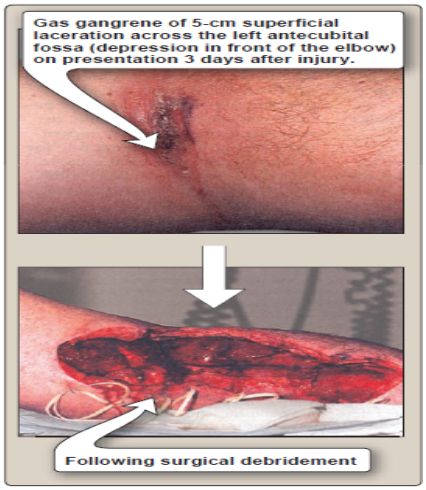


Figure 14.4
Gas gangrene of arm.

b. Anaerobic cellulitis: This is a clostridial infection of connective tissue in which the spread of bacterial growth along fascial planes (fasciitis) does not involve invasion of muscle tissue.

c. Foodborne infection: C. perfringens is a common cause of foodborne infection in the United States. Typically, the onset of nausea, abdominal cramps, and diarrhea occurs 8 to 18 hours after eating contaminated food. Fever is absent and vomiting rare. The attack is usually self-limited, with recovery within 1 to 2 days.

d. Necrotic enteritis: Outbreaks of a necrotizing bowel disease with high mortality (greater than 50 percent) .

e.Clostridial endometritis: This condition is a grave complication of incomplete abortion or the use of inadequately sterilized instruments. Gangrenous infection of uterine tissue is followed by illness due to toxins and bacteremia.

3. Laboratory identification: Diagnosis of clostridial myonecrosis or cellulitis rests largely on clinical presentation. With Gram stain, however, specimens from diseased tissue usually show vegetative clostridial forms (large, gram-positive rods), accompanied by other bacteria and cellular debris. When cultured anaerobically on blood agar, grows rapidly, producing colonies with a unique double zone of hemolysis due to production of α toxin (partial hemolysis) and perfringolysin O (complete hemolysis) as shown in Figure 14.5.

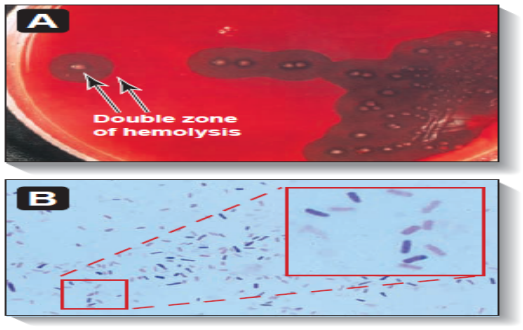


Figure 14.5
Clostridium perfringens. A. Colonies on blood agar showing double zone of hemolysis. B. Photomicrograph of Gram stain.

4-Treatment and prevention: The key to both prevention and treatment of gas gangrene is immediate and thorough removal of foreign material and devitalized tissue and exposure of the wound to O2. C. perfringens is sensitive to penicillin and several common inhibitors of prokaryotic protein synthesis.

C. Clostridium botulinum

C. botulinum causes botulism, which occurs in several clinical forms. Botulism is caused by the action of a neurotoxin that is one of the most potent poisons known and causes a flaccid paralysis.

1.Epidemiology: C. botulinum is found worldwide in soil and aquatic sediments, and the spores frequently contaminate vegetables and meat or fish.

2. Pathogenesis: There are several types of botulinum toxin, designated A through G, but human disease is almost always caused by types A, B, or E. Botulinum toxins affect peripheral cholinergic synapses by blocking the neuromuscular junction and inhibiting release of the neurotransmitter acetylcholine, preventing contraction and causing flaccid paralysis (Figure 14.6).

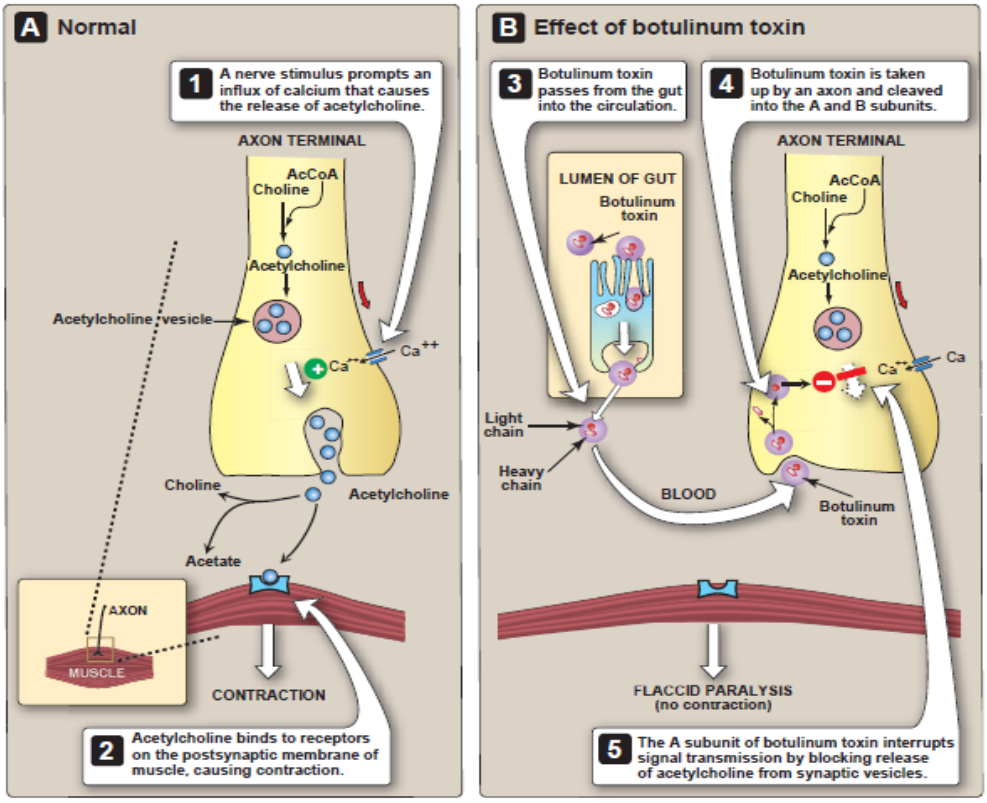


Figure 14.6
Mechanism of botulinum toxin. AcCoA = acetyl CoA.

3. Clinical significance:

a. Classic botulism: Food poisoning in which a patient first begins to experience difficulties in focusing vision, swallowing, and other cranial nerve functions, 12 to 36 hours after ingesting toxin-containing food but not necessarily viable organisms
is classic botulism. There is no fever or sign of sepsis. The patient usually succumbing to respiratory paralysis.
b-Infant botulism: The most common form of botulism in the United States today is infant botulism, or a cause of floppy baby syndrome. The condition is possibly a cause of sudden infant death syndrome.
c. Wound botulism: A rare form of botulism occurs when a wound becomes contaminated with the organism, and toxin is absorbed from that site.

4. Laboratory identification: The organism can be cultured and identified by standard anaerobic methods . Toxin is also identifiable in serum, stool, and food.

5. Treatment and prevention: Antitoxin (horse antiserum) that neutralizes unbound botulinum toxin should be administered as soon as possible in suspected botulinum intoxication. Proper food preservation techniques prevent the production of the clostridial exotoxin.

D. Clostridium tetani

The introduction of C. tetani spores into even small wounds via contaminated soil is probably a common occurrence. Growth of C. tetani is completely local, but it produces a powerful neurotoxin that is transported to the central nervous system, where it causes spastic paralysis.

1-Epidemiology: C. tetani spores are common in barryard, garden, and other soils. The most typical focus of infection in tetanus is a puncture wound caused, for example, by a splinter.

2. Pathogenesis: Tetanus toxin, called tetanospasmin, is an extremely potent toxin. It is transported from an infected locus by retrograde neuronal flow or blood. Binds irreversibly , penetrating neurons and blocks neurotransmitter release at inhibitory synapses, thereby causing severe, prolonged muscle spasms.

3. Clinical significance:

Tetanus

Caused by C. tetani spores infecting a puncture wound, a severe burn or postsurgical incision. In the early stages, the jaw muscles are affected, so that the mouth cannot open (**trismus**, or "lockjaw"). Gradually, other voluntary muscles become involved. Death is usually the result of paralysis of the chest muscles, leading to respiratory failure.

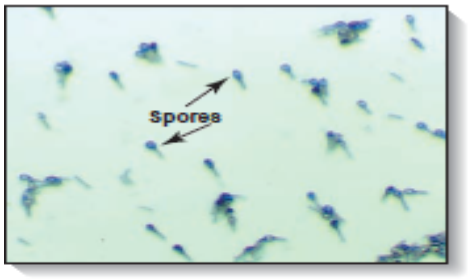


Figure 14.8
Photomicrograph of *Clostridium tetani* showing terminal spores.

4. Laboratory identification:

The diagnosis of tetanus is based largely on clinical findings. The focus of infection is often a trivial wound that may be difficult to locate. C. tetani has a characteristic morphology, with a as shown in Figure 14.8.

5- Ttreatment: Prompt administration of antitoxin to neutralize any toxin not yet bound to neurons is the first order of treatment. Treatment with human hyperimmune globulin (tetanus immune globulin) is preferred. Therapy includes treatment with sedatives and muscle relaxants to minimize spasms and attention to maintenance of ventilation.

6. Prevention: Active immunization with tetanus toxoid (formalininactivated toxin) prevents tetanus. It is usually administered to children as a triple vaccine with diphtheria toxoid and pertussis antigens (DTaP).

E. Clostridium difficile

Diarrhea, a common complication of antimicrobial drug treatment, can range from loose stools to life-threatening pseudomembranous

1. Pathogenesis: C. difficile is a minor component of the normal flora of the large intestine. Pathogenic strains produce two toxic polypeptides, designated toxins A and B. Toxin A is an enterotoxin that causes excessive fluid secretion, but also stimulates an

inflammatory response, and has some cytopathic effect in tissue culture. Toxin B is a cytotoxin. In tissue culture, it disrupts protein synthesis and causes disorganization of the cytoskeleton.

2. Clinical significance:
Virtually all antimicrobial drugs have been reported as predisposing to clostridial AAD and colitis . The three drugs most commonly implicated are clindamycin, ampicillin, and the cephalosporins. The severity of disease
varies widely from mild diarrhea through varying degrees of
inflammation of the large intestine to a fulminant PMC.

3. Laboratory identification:
C. difficile can be cultured from stools and identified by routine anaerobic procedures, but the more rapid and useful tests are directed at demonstrating toxin production in
stool extracts. Enzyme immunoassays fo r exotoxins A and B have replaced earlier immunologic or tissue culture cytotoxicity assays.

4. Treatment: Discontinuance of the predisposing drug and fluid replacement usually lead to resolution of the symptoms. Relapses, however, are common. Oral administration of metronidazole or vancomycin is usually added .

III. ANAEROBIC GRAM-NEGATIVE RODS

Anaerobic gram-negative rods are normally the most common organisms
in the oral cavity (particularly the gingiva), female genital tract, and lower GI tract. Gram-negative rods generally constitute the majority of organisms associated with anaerobic abscesses. A localized abscess is the most common lesion, and the infectious process often involves two or more species of organisms. For example, various facultative organisms help lower the pO2, thus providing the anaerobic environment required by the coinfecting gram-negative rods (Figure 14.11).

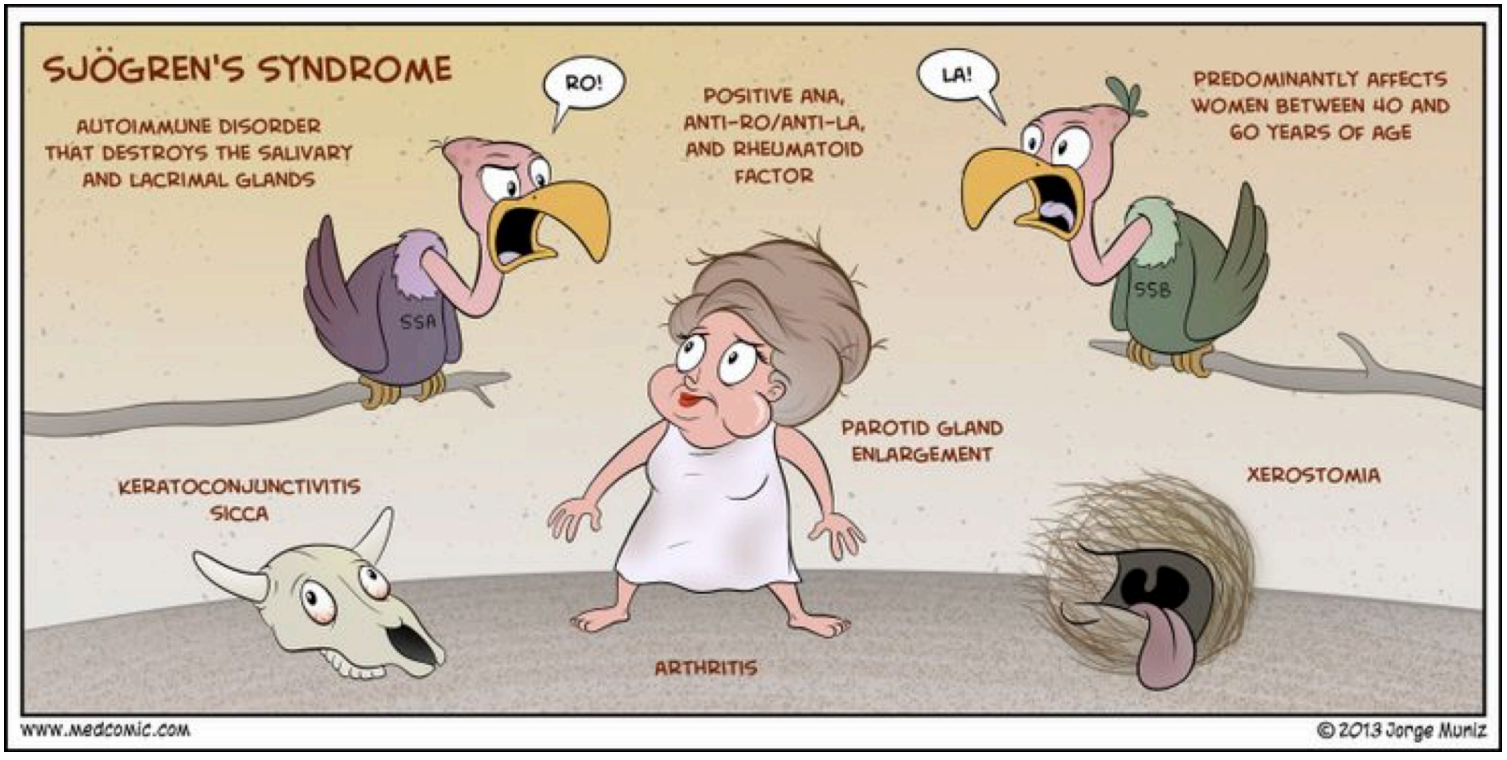
A. Bacteroides
Members of the genus Bacteroides are the predominant anaerobes found in the human colon. They are part of the normal flora and only cause disease when they gain access to tissues or the blood during bowel penetration (for example, during surgery or trauma). They are, however, the most common cause of serious infections by anaerobic organisms. Bacteroides are slender rods or cocco - bacilli. Their polysaccharide capsule is an important virulence factor, conveying resistance to phagocytosis.

1. Epidemiology: Bacteroides are transmitted from the colon to the blood or peritoneum following abdominal trauma. Therefore, the source of infection is endogenous (it is not transmitted from person to person).
2. Pathology and clinical significance: The major disease-causing Bacteroides species is Bacteroides fragilis. When released from the colon into the blood, B. fragilis multiplies

rapidly, causing bacteremia. If it is introduced into the abdominal cavity, B. fragilis causes peritonitis, and/or abdominal abscesses.

3. Laboratory identification: Exudates from mixed anaerobic lesions are often copious and noticeably foul smelling. A Gram stain of such exudates shows numerous faint, slender, gram-negative rods, usually in mixed flora. The organisms are easily obscured by debris and polymorphonuclear leukocytes. B. fragilis can be cultured
on blood agar under anaerobic conditions

4-Treatment and prevention: Drug resistance is common among the Bacteroides. Metronidazole is the antibiotic of choice for B. fragilis infections. Alternative choices include ampicillin-sulbactam imipenem-cilastatin, ticarcillin-clavulanate, cefoxitin, or clindamycin. To prevent Bacteroides contamination of a surgical wound, a perioperative antibiotic, such as cefoxitin, can be administered.



CHAPTER 15
Spirochetes

Spirochetes are long, slender, motile, flexible, undulating, gram-negative bacilli that have a characteristic corkscrew or helical shape.

STRUCTURAL FEATURES OF SPIROCHETES:
(السمات الهيكلية اللولبيات)

The spirochete cell has a central protoplasmic cylinder bounded by a plasma membrane and a typical gram-negative cell wall. This cylinder is enveloped by an outer membrane composed of glycolipids and lipoproteins. Between the peptidoglycan and the outer sheath are located multiple periplasmic flagella that do not protrude from the cell but are oriented axially. Spirochetes can move through highly viscous solutions with little impediment, and it is theorized that this kind of motion is responsible for the ability of spirochete pathogens to penetrate and invade host tissue.

TREPONEMA PALLIDUM:(اللولبية الشاحبة)

Syphilis is primarily a sexually transmitted infection caused by the spirochete T.pallidum. The causative organism of syphilis is extremely fastidious and fragile. It cannot be cultured in cell-free systems and is sensitive to disinfectants, heat, and drying. Unlike typical gram-negative bacteria, most spirochetes, including T. pallidum do not have LPS, or endotoxin, in the outer leaflet of the outer membrane.

A. Pathogenesis:
Transmission of T. pallidum is almost always by sexual contact or transplacentally (congenital syphilis).

B. Clinical significance:
1- Syphilis: Syphilis occurs in three stages

The first stage	The secondary stage	The tertiary stage
Symptom of primary syphilis is a hard, painless genital or oral ulcer (chancre) that develops at the site of inoculation.	This stage is characterized by the appearance of a red, maculopapular rash on almost any part of the body, including the palms of the hands and soles of the feet. Also present are pale, moist, flat papules seen primarily in the anogenital region (where they are called condylomata lata) armpits, and mouth.	Characterized by degeneration of the nervous system; cardiovascular lesions, such as ascending aortic aneurysms; and granulomatous lesions (gummas) in the liver, skin, and bones.

* *Both primary and secodary lesion are extremely infectious.*

2-Congenital syphilis: T. pallidum can be transmitted through the placenta to a fetus after the first 10 to 15 weeks of pregnancy. Infection can cause fetal or infant death or spontaneous abortion.

D. Treatment and prevention:

One single treatment with penicillin is curative for primary and secondary syphilis, and no antibiotic resistance has been reported. In cases of patient sensitivity to penicillin, alternate therapy with erythromycin or tetracyclines may also be effective. There is no vaccine against T. pallidum, and prevention depends on safe sexual practices.

BORRELIA BURGDORFERI:

(بوريليا)

Members of the genus Borrelia are relatively large spirochetes which like Treponema, have endoflagella that make them highly motile. Borrelia species are unusual among bacteria in that they have linear rather than circular plasmid and chromosomal DNA. Like T. pallidum, Borrelia do not produce endotoxin or exotoxins.

A.Pathogenesis:

Lyme disease is caused by the spirochete B. burgdorferi, which is transmitted by the bite of a small tick of the genus Ixodes.

B. Clinical significance:

The first stage	The second stage	The third stage
Of Lyme disease begins 3 to 32 days after a tick bite, when characteristic red, circular lesion with a clear center (erythema migrants) appears at the site of the bite (Figure 15.9). Flulike symptoms often accompany the erythema.	Of the disease begins, with symptoms such as arthritis, arthralgia, cardiac complications, and neurologic complications such as meningitis.	Begins with the appearance of chronic arthritis, progressive CNS disease, chronic skin manifestations, and cardiac dysfunction

D. Treatment and prevention

Doxycycline is the most recommended treatment for the early stages of the disease. If arthritic symptoms have already
appeared, longer courses of antibiotics (ceftriaxone) are used.
Prevention of infection also includes use of insect repellents and
wearing clothing that sufficiently protects the body from tick bites.

RELAPSING FEVER SPIROCHETES:

(الحمى الراجعة اللولبيات)

Fever can be caused by a variety of Borrelia species, including:

1- B. hermsii.
2- Borrelia parkeri.
3- Borrelia turicatae.

A. Clinical significance:

The first symptoms of relapsing fever appear 3 to 10 days after exposure to an infected arthropod. These symptoms include an abrupt onset of high fever accompanied by severe headache, muscle pain, and general malaise. In fetal cases, the spirochete invades many organs of the body, with death generally due to myocarditis with shock.

B. Diagnosis and treatment

Diagnosis is usually based on the appearance of Giemsa- or Wright stainable. The relapsing nature of the disease makes it difficult to distinguish spontaneous remissions from response to therapy. No vaccines are available.

LEPTOSPIRA INTERROGANS:

L. interrogans infection causes the disease leptospirosis. L. interrogans is sensitive to drying and a broad range of disinfectants. It can, however, survive for weeks in slightly alkaline water.

A. Epidemiology and pathogenesis:

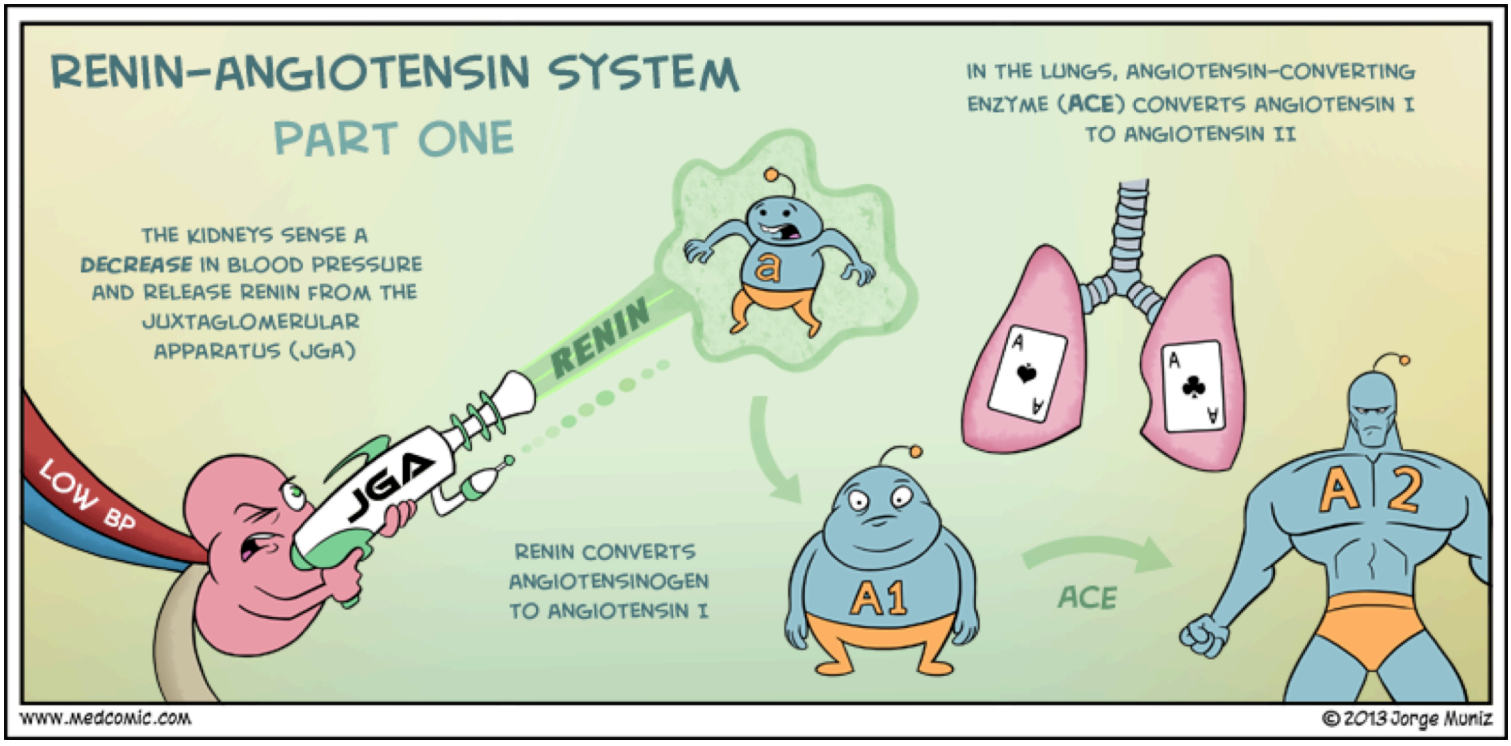
Leptospirosis is essentially an animal disease that is coincidentally transmitted to humans, primarily by water or food contaminated with animal urine. Entrance to the body can also occur via small skin abrasions or the conjunctiva.

B. Clinical significance:

Accompanied by invasion of the liver, kidneys, and CNS. This results in jaundice, hemorrhage, tissue necrosis, and/or aseptic meningitis. This second stage of the disease, involves a rise in circulation IgM antibodies.

C. Diagnosis and treatment:

Penicillin or doxycycline is useful if administered during the first stage of the disease. No vaccine is currently available.



CHAPTER 16

Mycoplasma

Mycoplasmas: are small, prokaryotic organisms with no peptidoglycan their cell walls.

II. GENERAL FEATURES OF MYCOPLASMAS

Lacking cell walls, mycoplasmas are enclosed instead by a membrane

composed of a lipid bilayer. They are, therefore, plastic and pleomorphic

and thus cannot be classified as either cocci or rods . Mycoplasmas are also the smallest of

known free-living, self-replicating prokaryotic cell

A. Physiology

Mycoplasmas have limited biosynthetic capabilities and require a

.variety of small, organic molecules for growth. Unlike other prokaryotes .

B. Colony production

Mycoplasmas produce minute colonies on specialized agar after several days of incubation. . These are best visualized under 30× to 100× magnification. The central portion of the colony penetrates the agar, whereas the periphery spreads over the adjacent surface, in some cases giving the colony a characteristic “fried egg” appearance.

III. MYCOPLASMA PNEUMONIAE

M. pneumoniae is transmitted by respiratory droplets and causes a

lower respiratory tract infection (atypical pneumonia, so named

(because the signs and symptoms are unlike typical lobar pneumonia

The organism accounts for approximately 20 percent of pneumonia

,cases as well as causing milder infections such as bronchitis, pharyngitis

and nonpurulent otitis media. The highest incidence

of clinical disease is seen in older children and young adults ages(6 to 20 years).

B. Clinical significance

Atypical pneumonia (lower respiratory tract disease) is the bestknown form of M.

symptoms such as

1-unrelenting headache, accompanied by fever

2-chills

3- malais

After 2 to 4 days

1-a dry or scantily productive cough develops..

.2- Earache is sometimes.

3-chest radiographs reveal a patchy .

C. Immunity

.Infection with M both local and systemic immune responses . Serum antibody to outer membrane glycolipids and to the P1 adhesin can be demonstrated, with antibody peaking 2 to 4 weeks after infection and gradually disappearing over the following year. An immunoglobulin M antibody, the cold agglutinin, is produced by approximately 60 percent of infected patients. [Note: This antibody's name derives from the fact that it reacts with the human erythrocyte antigen I, reversibly agglutinating I+ red blood cells at temperatures of 0oc to 4oc but not at 37oc Some patients develop very high titers of cold agglutinins. With exposure to cold temperatures this may result in ischemia and even necrosis of distal extremities hands and feet because of in vivo clumping of red blood cell.

D. Laboratory identification

Direct microscopic examination of clinical material for M. serologic test is the most used pro cedures of atypical pneumonia ..

E. Treatment

M. pneumoniae is sensitive to doxycycline, azithromycin, or levofoxacin

When given early, antibiotic treatment

shortens the course of disease, although symptoms may be eliminated

only gradually. The organisms, however, may persist in the

convalescent upper respiratory tract for weeks. Because there is no

,rapid way to make the diagnosis of M. pneumoniae pneumonia

treatment begins with empiric therapy (most often with macrolide

antibiotics) for atypical pneumonia.

IV. GENITAL MYCOPLASMAS

Three Mycoplasma species

M. hominis

U. urealyticum

M. genitaliu

are human urogenital pathogens. They are often associated with

sexually transmitted infections, such as NGU or puerperal infections

(that is, infections connected with, or occurring during childbirth or the

period immediately following childbirth)

A. Mycoplasma hominis and Ureaplasma urealyticum.

U. urealyticum

• Endometritis.

U. urealyticum

• Urethritis.

M. hominis.

• Postabortal/postpartum fever.

• Pelvic inflammatory disease.

B. Mycoplasma genitalium

M. genitalium has been recognized as a sexually transmitted

pathogen, resulting in a series of syndromes similar to those caused

by Neisseria gonorrhoeae and Chlamydia trachomatis

M. genitalium causes NGU in males and is associated)

with cervicitis and PID in women. The organisms appear to be resistant

to doxycycline, which is the treatment of choice for NGU caused

.by C. trachomatis. Therefore, recommendations for testing for M

genitalium include cases in which the patient fails to respond to

doxycycline treatment. PCR amplification is recommended for specific

diagnosis of M. genitalium infections. Azithromycin is effective

for treating M. genitalium infections.

V. OTHER MYCOPLASMAS Several other species of mycoplasmas can be recovered from human sources. No pathogenic role has been established to date for these organisms. One such organism, AIDS-associated mycoplasma, orMycoplasma incognitus, has been isolated in high frequency from HIVpositive patients, in which the organism may play a role, possibly as a secondary invader.

CHAPTER 17

Chlamydiae

The family Chlamydiaceae consists of small bacteria that are obligate intracellular parasites, depending on the host cell for energy in the forms of adenosine triphosphate ((ATP) and nicotinamide adenine dinucleotid NAD+).Figure 17.1 summarizes the clinically significant chlamydiae.

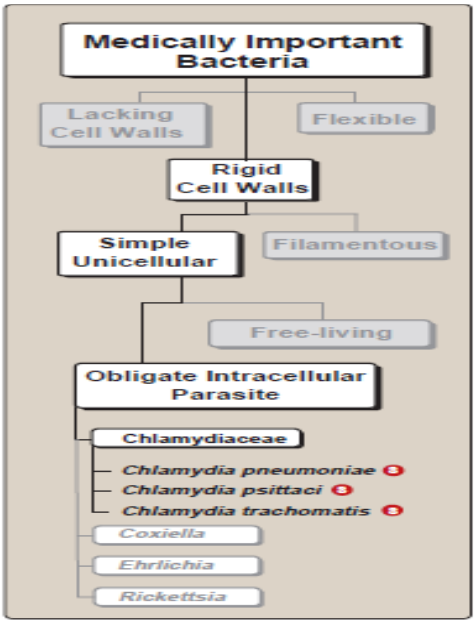


Figure 17.1
Classification of *Chlamydia*.
See pp. 335–336 for summaries of these organisms.

GENERAL FEATURES OF CHLAMYDIAE:

Chlamydiae are small, round-to-ovoid organisms that vary in size during the different stages of their replicative cycle. Cell envelope consists of two lipid bilayers resembling a gram-negative envelope. Cell wall active antimicrobials have negative impacts on the life cycle of the chlamydiae. They synthesize their own proteins and, therefor, are sensitive to antibiotics that inhibit this process, such as tetracyclines and macrolides.

A. Physiology:

They are unable to synthesize their own pools of ATP or regenerate NAD+ by oxidation. With these high-energy molecules exogenously supplied, chlamydiae produce CO2 from compounds such as glucose.

B. Pathogenesis:

Chlamydiae have a unique life cycle, with morphologically distinct infectious and reproductive forms (Figure 17.3).

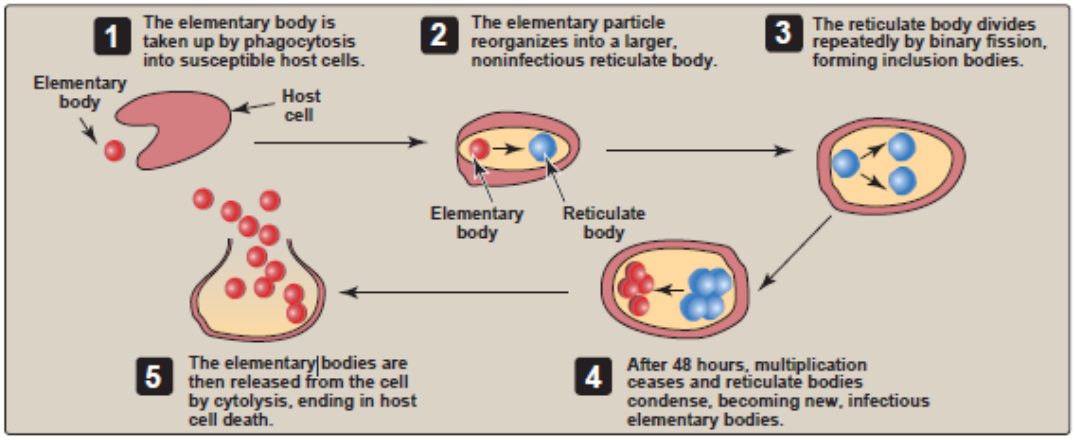


Figure 17.3
Reproductive cycle of *Chlamydiaceae*.

C. Laboratory identification:

Useful stains:	Chlamydial antigens:
Can be visualized under light microscopy by stains that pre-serve the host cell architecture. Direct immunofluorescence is also a common and useful procedure.	**Although DNA identity among the family Chlamydiaceae is less than 30 percent, they share lipopolysaccharide antigens. Antigenic classification in this genus is usually done by immunofluorescence, using monoclonal .antibodies**

CHLAMYDIA TRACHOMATIS:

Is divided into a number of serotypes, which correlate with the clinical syndrome they cause.

For example:

C. trachomatis the major causal agent of the syndrome NGU.

A. Clinical significance:

C. trachomatis causes a range of GU and eye infections.

1. Nongonococcal urethritis	2- Lymphogranuloma venereum:	3. Trachoma: (التراخوما)	4. Neonatal conjunctivitis and other infections: (التهاب الملتحمة الوليدي)	5. Inclusion conjunctivitis in adults:
C. trachomatis infections are sexually active individuals of all socioeconomic ,groups. In men the urethra is the initial site of infection. Women may present with cervicitis and/or urethritis. Infection may climb to the top Reproductive system. NGU is symptomatically similar to infections caused by Neisseria gonorrhoeae. Repeated or chronic episodes may lead to infertility in both sexes.	C.trachomatis serotypes L1, L2,and L3 cause lymphogranuloma venereum (LGV), a more invasive sexually transmitted disease. LGV is characterized by transient papules on the external genitalia. followed in 1 to 2 months by painful swelling of inguinal and perirectal lymph nodes. The inguinal ligament often forms cleft known as the “groove sign” between masses of inguinal lymph node.	c.trachomatis serotypes A, B, Ba, and C cause a chronic keratoconjunctivitis that often results in blindness. Trachoma is transmitted by personal contact, ,for example from eye to eye via droplets.	Over 50 percent of infants born to women infected with C. trachomatis . will contract symptomatic infection on passage through the birth canal. Usually heals After appropriate antimicrobial therapy, without permanent damage to the eye.	**Individuals of any age may develop transient purulent conjunctivitis caused by C. trachomatis serotypes D–K.**

B. Laboratory identification:

C. trachomatis can be demonstrated in clinical material by several direct procedures and by culturing in human cell lines.

1- Direct tests: Microscopic examination using direct fluorescent antibody. C. trachomatis infections can be detected with high sensitivity and specificity using DNA amplification performed on urine specimens.

2- Culturing methods: C. trachomatis can be cultivated by tissue culture in several human cell lines. In standard procedure using McCoy cells, addition to culture medium of eukaryotic metabolic inhibitor, such as cycloheximide, enhances growth of parasite.

3- Detection of serotypes: Serotypes of C. trachomatis can be determined by immunofluorescence staining with monoclonal antibodies.

C. Treatment and prevention:

Chlamydiae are sensitive to a number of broad-spectrum antibacterials. Azithromycin and tetracycline are currently the drugs of choice. Erythromycin should be used in small children and pregnant women because of the effects of tetracyclines on teeth and bones.

CHLAMYDIA PSITTACI:

(المتدثرة الببغائية)

Psittacosis, also known as ornithosis, denotes a zoonotic (animal) disease that is transmitted to humans by inhalation of dust contaminated with respiratory secretions or feces of infected birds. The human disease usually targets the lower respiratory tract. There is an acute onset of fever, hacking dry cough, and flulike symptoms. Bilateral patchy pulmonary infiltrates are observed. Enlargement of liver and spleen is a frequent accompanying feature. Doxycycline or erythromycin is effective in eradicating symptoms, but the organisms sometimes persist well into convalescence, because the drugs are bacteriostatic, not bactericidal.

CHLAMYDIA PNEUMONIAE:

pneumoniae is a respiratory pathogen causing pharyngitis, sometimes followed by laryngitis, .B bronchitis, or interstitial pneumonia. It is a significant cause of community-acquired respiratory infection. The organism is sensitive to doxycycline and erythromycin.

CHAPTER 18
(Mycobacteria and Actinomycetes)

Medically Important Bacteri:

Lacking:

- Cell Walls

- flexible

- Simple Unicellular Filamentou

Types of bacteria
Mycobacteria
Mycobacterium abscessus
Mycobacterium aviumintracellulare
Mycobacterium bovis
Mycobacterium chelonei
Mycobacterium fortuitum
Mycobacterium kansasii
Mycobacterium leprae
Mycobacterium marinum
Mycobacterium scrofulaceum
Mycobacterium tuberculosis
Mycobacterium ulcerans
Actinomycetes
Actinomyces israelii
Nocardia asteroides
Nocardia brasiliensis

Mycobacteria are slender rods with lipid-rich cell walls that are resistant to penetration by chemical dyes.

MYCOBACTERIA:

A. Mycobacterium tuberculosis Acid-fast stain of sputum from a patient with tuberculosis. B. Typical growth pattern showing “cording” that is, growing in strings incidence of new cases of tuberculosis (United States) Progression of active tuberculosis infection

Pathogenicity: Tubercle bacilli are inhaled into the alveoli of the lung and ingested by macrophages ,but are not killed. Tubercle bacilli multiplying in macrophages cause additional macrophages to migrate into the area, forming an early tubercle. After a few weeks, many of the macrophages die, releasing tubercle bacilli and forming a caseous center in the tubercle, which is surrounded by a mass of macrophages and lymphocytes. The disease may become dormant after this stage. In some individuals, a mature tubercle is formed, as a firm outer layer containing fibroblasts surrounds the mass of macrophages and lymphocytes. The caseous center enlarges by the process of liquefaction, forming a tuberculous cavity in which the bacilli multiply. Liquefaction continues until the tubercle ruptures, allowing bacilli to spill into the bronchiole and be disseminated throughout the respiratory system and other systems of the body

Stages in the pathogenesis of tuberculosis (TB)

Primary tuberculosis
- TB skin test negative
- Radiograph negative

Latent-dormant tuberculosis
- TB skin test positive
- Radiograph negative for active disease

Secondary (reactivation) tuberculosis
- TB skin test positive
- Radiograph positive
- Sputum positive

No disease Progressive primary (active) infection

- TB skin test positive
- Radiograph positive
- Sputum positive

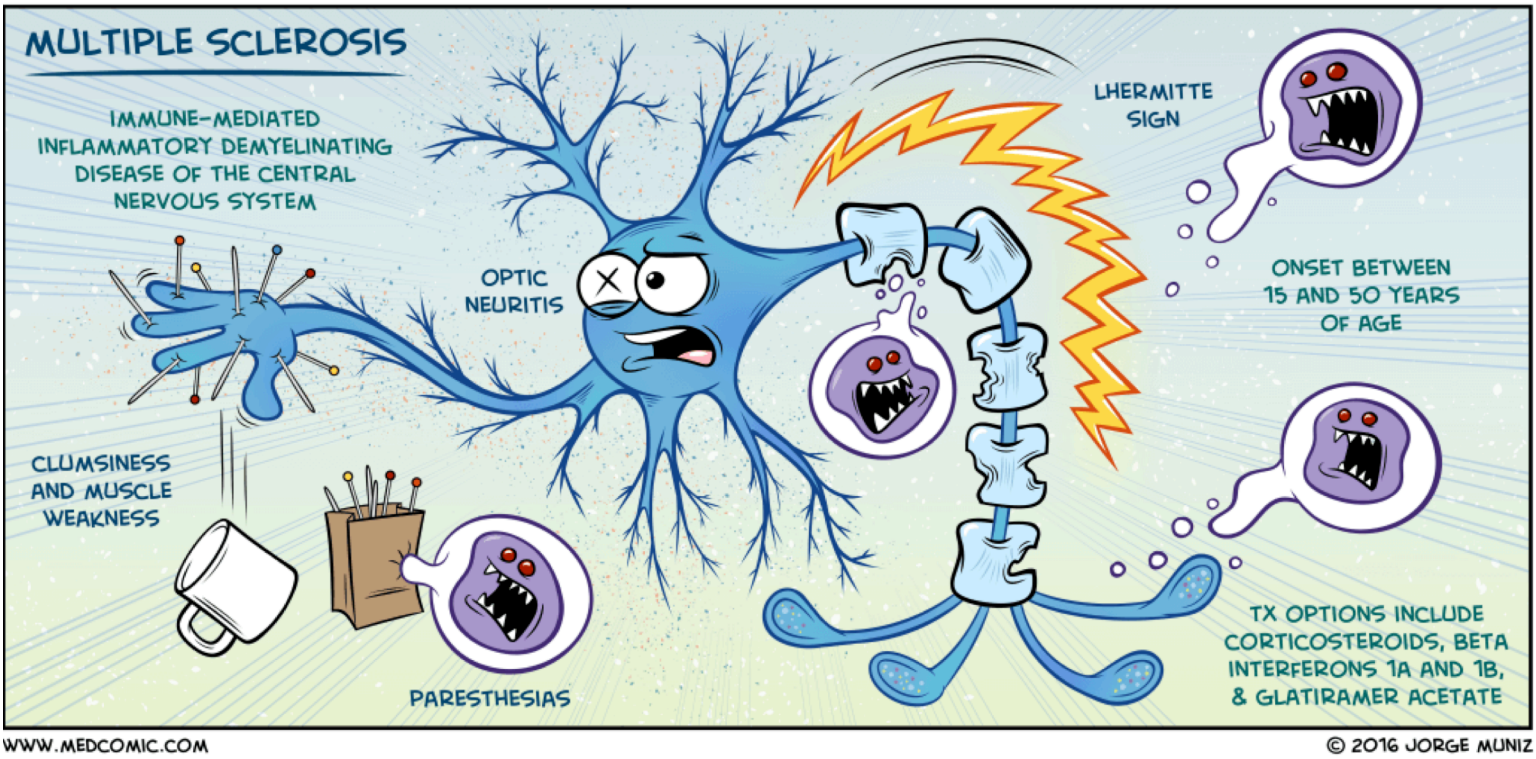
Treatment: Several chemotherapeutic agents are effective against M. tuberculosis. Because strains of the organism resistant to a particular agent emerge during treatment, multiple drug therapy is employed to delay or prevent emergence. **Isoniazid, rifampin, ethambutol, streptomycin, and pyrazinamide** are the principal or “first-line” drugs because of their efficacy and acceptable degree of toxicity.

ACTINOMYCETES are a group of filamentous, branching, gram-positive organisms that easily fragment into slender rods

A. Actinomyces israelii

B. Nocardia asteroides and Nocardia brasiliensis

ATYPICAL MYCOBACTERIA are distinct from classical mycobacteria in that they are widespread in the environment and are not pathogenic in rodent animal models. The atypical mycobacteria are classified into four groups (Runyon groups I–IV) based upon several phenotypic character- istics, including pigment production and growth rate.



CHAPTER 19

Rickettsia, Erhlichia, Anaplasma and

Rickettsia, Ehrlichia, Anaplasma, and Coxiella have a number of features in common
For example:

1-They grow only inside living host cells.

2- Most infections are transmitted by infected arthropods vectors.

3- Diseases caused by these organisms, such as typhus, spotted fever.

RICKETTSIA:

Rickettsia have the structural features of typical prokaryotic cells. They are small, rodlike or coccobacillary shaped, and have a typical double-layered, gram-negative cell wall, are best visualized under the light microscope with one of the polychrome stains such as Giemsa or Macchiavello.

A. Physiology:

The obligate requirement for an intracellular environment for rick-ethical replication is not fully understood, but its plasma membrane is leaky and, therefore, easily permeable to host cell nutrients and coenzymes. Rickettsia contain a number of antigens that convey both group and species specificity.

B. Pathogenesis:

Rickettsia are transmitted to humans by arthropods, such as fleas ticks, mites, and lice. Depending on the rickettsial species, rodents humans, or arthropods can serve as reservoirs of infectious organisms. Following a bite by an infected arthropod, the organisms are taken into cells by a process similar to phagocytosis. The organisms degrade the phagosome membrane by production of a phospholipase C.

C. Clinical significance—spotted fever group:

1- Rocky Mountain spotted fever: The disease is characterized by high fever and malaise followed by a prominent rash that is initially macular but may become petechial or frankly hemorrhagic. The rash typically begins on the extremities, involving the palms and soles, and develops rapidly to cover the body. In untreated cases

vascular disturbances leading to tissue infraction and myocardial or renal failure may ensue.

2- Other spotted fevers: Tickborne spotted fevers similar to Rocky Mountain spotted fever are found in several regions of the world. They vary in severity and are caused by organisms such as Rickettsia conorii, Rickettsia canadensis, and Rickettsia sibirica.

C. Clinical significance—typhus group:

1. Louseborne (epidemic) typhus:

Louseborne typhus is caused by Rickettsia prowazekii.

Note: Epidemic typhus is a different disease from salmonella-induced typhoid fever.

R. prowazekii is transmitted from person to person by an infected human body louse that excretes organisms in its feces. Scratching louse bites facilitates the introduction of the pathogen from louse feces into a bite wound.

a. Typhus epidemics:

Typhus occurs most typically in large epidemics under conditions of displacement of people, crowding and poor sanitation. Clinical symptoms of typhus develop an average of 8 days after infection and include high fever; chills; severe headache and, often, a considerable degree of prostration and stupor. Complications of epidemic typhus may include CNS dysfunction, myocarditis, and death.

b. Brill-Zinsser disease (recrudescent typhus):

This is a usually milder form of typhus that occurs in persons who previously recovered from primary infections (10 to 40 years earlier).

2- Other forms of typhuslike fever: Murine (endemic) typhus, caused by Rickettsia typhi, is a clinically similar but usually milder disease than that caused by R. prowazekii. Human infections are initiated by the bites of infected rat fleas.

D. Laboratory identification:

Suspensions or soluble extracts of rickettsia are used to demonstrate group- and species-specific antibodies by indirect immunofluorescence. Alternatively although not widely available, infected cells can be detected by immunofluorescence or histochemical procedures on some clinical samples such as punch biopsies from areas of rash .

E. Treatment:

Doxycycline is the drug of choice for the treatment of Rocky Mountain spotted fever in both adults and children, except for pregnant women who should be treated with chloramphenicol . The decision to treat must be made on clinical grounds, together with a history or suspicion of contact with an appropriate arthropod vector, before the seroconversion data are available .

F. Prevention of infection:

Prevention depends on vector control, for example, delousing rodent-proofing buildings, or clearing brush in tick- or mite-infested areas as appropriate .

EHRLICHIA AND ANAPLASMA:

Ehrlichia and Anaplasma resemble Rickettsia in appearance and

,behavior. However, these organisms parasitize monocytes and neutrophils

respectively, and grow exclusively within host-derived cytoplasmic

vacuoles, creating characteristic inclusions called morulae .

A. Clinical significance:

Human monocytic ehrlichiosis (HME) is caused by Ehrlichia chaffeensis Human granulocytic anaplasmosis (HGA) is caused by the organism Anaplasma phagocytophilum . The symptoms of HME and HGA are similar and often nonspecific. Common symptoms include fever, chills, headache, myalgia, and arthralgia . More severe manifestations of HME include meningoencephalitis, myocarditis and acute renal failure . Serious manifestations of HGA include severe leukocytopenia and thrombocytopenia due to damage of the infected cell

populations .

B. Laboratory identification:

Antibody assays and a PCR method have been diagnostically useful in investigative laboratories. Occasionally, the characteristic morulae can be seen in peripheral blood smears during acute illness.

C. Treatment:

The treatment of choice is doxycycline.

COXIELLA

Coxiella burnetii, the causal agent of Q fever.

It has several features that distinguish it from other rickettsia. For Example:

1- It grows in cytoplasmic vacuoles and seems to be stimulated by the low pH of a phagolysosome, being resistant to the host degradative enzymes within that structure .

2- it is extremely resistant to heat and drying and can persist outside its host for long periods.

3- it causes disease in livestock, such as cattle and in other mammals, but is not transmitted to humans by arthropods.

human infection usually occurs following inhalation of infected dust in .

A. Clinical significance:

Classic Q fever is an interstitial pneumonitis (not unlike some viral or mycoplasmal ,illnesses) that may be complicated by hepatitis
myocarditis, or encephalitis. C. burnetii should also be considered as a potential causative agent in culture-negative endocarditis .

B. Laboratory identification:

Serologic assays are the principal means of specific diagnosis, and serologic surveys indicate that inapparent infections are common.

C. Treatment and prevention:

Doxycycline is the drug of choice for treatment. A vaccine has been reported to be of limited use in occupationally exposed individuals, but it is not readily available in the United States.

CHAPTER 20

Fungi

Overview:

fungi(الفطريات)are a diverse group of saprophytic(رِمِّيّ ، رَمّام deriving nourishment from dead organic matter) and parasitic eukaryotic organisms(كائنات طفيلية حقيقية النواة).Virtually all organisms are subject to fungal infection. Of some 200000 fungal species, only about 100 have pathogenic potential for humans. Only a few of these species account for most clinically important fungal infections (figure 20.1). Human fungal diseases (mycoses- داء فطري) are classified by the location on or in the body where the infection occurs

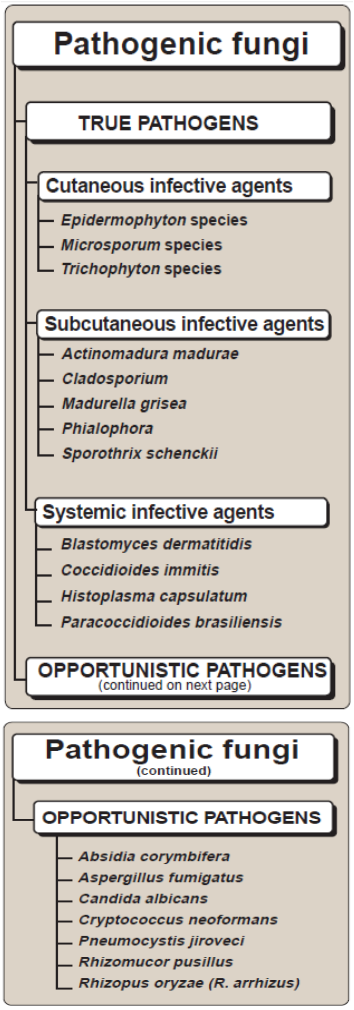


Figure 20.1 (continued)
Classification of pathogenic fungi.

Name		Location
1-Cutaneous mycoses	Limited to the	epidermis
2-Subcutaneous mycoses	Beneath the	Skin
3-Systemic mycoses	Deep within the	Body
	Disseminated to	Internal organs

II. Characteristics of major fungal groups: Fungi are eukaryotes.

A. Cell wall and membrane components :

fungal cell walls are composed largely of chitin(a polymer of N-acetylglucosamine)therefore, unaffected by antibiotics. And it contains ergosterol which is a vital component of fungal cell membranes, disruption of its biosynthesis results in cell death . these chemical characteristics are useful in targeting chemotherapeutic agents against fungal infections. Many such agents interfere with fungal membrane synthesis or function .

B. Habitat and nutrition

Natural Habitat	Majority	Soil - water containing decaying organic matter.
	Some	Parasitic on living organisms.
Nutrition	All fungi are chemoheterotrophs (requiring some preformed organic carbon source for growth).	
	Fungi don't ingest (it depend upon transport of soluble nutrients-it obtain these by secrete degradative enzymes into their immediate environment-across their cell membranes).	

C. Modes of fungal growth

1-Filamentous (mold like) fungi(الفطريات الخيطية)	It's thallus(الجسم الخضري)is a mass(mycelium) of threads(hyphae) with many branches, it grows by branching & tip elongation .the hyphae are partitioned into segments (septate)which is perforated, and in other fungi are uninterrupted by crosswalls(nonseptate).
2-Yeast(خميرة) like fungi	It exist as populations of single ,unconnected ,spheroid cells. And these fungi reproduce by budding.
3-Dimorphic (مزدوج الشكل) fungi	It cause systemic mycoses ,being yeast-like in one environment and mold-like in another, according to the temperature and carbon dioxide level .

D. Sporulation: by which fungi reproduce (spread through the environment).

1- Asexual Sporulation: Asexual spores (conidia) are formed by mitosis in or on specialized hyphae (conidiophores). Because the conidia are easily detached from their underlying mycelial mats, conidia can become airborne and cause fungal infection.

2- Sexual Sporulation : This process is initiated when a haploid nucleus from each of two compatible strains of the same species fuse to form a transient diploid. The products become sexual spores.

E. Laboratory identification :1.The standard medium is sabouraud dextrose agar,which ,because of its low pH(5.0),inhibits bacterial growth while allowing fungal colonies to form . 2.Identification is based on the microscopic morphology of conidial structures. 3.Clinical samples may be pus,blood,spinal fluid,or skin scrapings.These specimens can also be evaluated histologically by direct staining. 4.Serologic tests and immunofluorescent techniques are also useful in identification.

III. Cutaneous (dermatophytoses) mycoses: It caused by the dermatophytes which fall into : Trichophyton, Epidermophyton , and Microsporum.

A. Epidemiology

The causative organisms of the dermatophytoses are distinguished by there NATURAL HABITATS:		
Anthropophilic(residing on human skin)	Zoophilic(on domestic &animals skin)	Geophilic (in the soil)
Most human infections		
Transmission is by infected skin scales on		

B. Pathology: dermatophytes use keratin as a source of nutrition, So they infect keratinized tissues and structures.

C. Clinical significance: itching, scaling skin patches –can be inflamed and weeping. Some organisms can cause more than one disease ,depending on the site of infection or condition of the skin .The following re the most commonly encountered Dermatophytoses :

Name	Subtypes	Site	Apperance
1-Tinea pedis (athlete's foot)	-Trichophyton rubrum -Trichophyton mentagrophytes -Epidermophyton floccosum.	Between the toes but can spread to the nails.	Yellow and brittle.
2-Tinea corporis(ringworm)	-E. floccosum -Trichophyton -Microsporum	Any site of the body	Rings with scaly centers
3-Tinea capitis(scalp ringworm)	-Trichophyton -Microsporum	Scalp	Range from small ,scaling patches to involvement of the entire scalp.
4- Tinea cruris(jock itch)	-E.floccosum -T.rubrum	Moist groin area	Similar to ringworm
5- Tineaunguium (onychomycosis)	-T.rubrum	Nails	Nails thicken &become discolored &brittle.

D. Treatment :

Removal of infected skin, Followed by topical application of antifungal antibiotics. Infections of the hair and nails usually require (oral) therapy.

IV. Subcutaneous Mycoses: Are fungal infections of the dermis, subcutaneous tissue, and bone .Causative organisms reside in the soil and decaying or live vegetation.

IV. Subcutaneous mycoses: are fungal infections of the dermis, Subcutaneous tissue, and bone .Causative organisms reside in the soil and decaying or live vegetation.

A. Epidemiology: it acquired through traumatic lacerations or puncture wounds.And they are not transmissible from human.
B. Clinical significance: The common subcutaneous mycoses in tropical and subtropical regions.

Name	Subtypes	Appearance
1-Sporotrichosis	- Sporothrix schenckii	Granulomatous ulcer at the puncture site.
2-Chromomycosis	For example: -Phialophora -Cladosporium	Warty nodules that spread slowly along the lymphatics & develop crusty abscesses.
3-Mycetoma (Madura foot)	-Madurella grisea -Exophiala jeanselmi.	A localized abscess(discharges pus, serum & blood through abnormal channel), usually on the feet.

v.Systemic mycoses

True pathogens	Opportunistic pathogens
Infect normal healthy individuals.	Primarily infect debilitated and/or immunocompromised individuuals.

A. Epidemiology and pathology : it enter the host by inhalation of airborne spores,which germinate in the lungs and from it to any organ of the body.
B. Clinical significance: Healthy patients present only mild symptoms & self-limiting .In immunosuppressed patients it can be life threatening.

1-Coccidioidomycosis:Caused by coccidioides immitis. It cause fever & respiratory illness. The lesions occur most often in the bones and the central nervous system.

2-Histoplasmosis:Caused by Histoplasma capsulatum. It enter the lungs. Pulmonary infections may be acute but relatively benign and self-limiting ,or they can be chronic, progressive, and fatal(dissemination is rare).Definitive diagnosis is by(isolation and culture of the organism or by detection of exoantigen in urine specimens).Soils that are laden with bird, chicken, or bat droppings are a rich source of H.capsulatum.Clinical manifestations are wide but often resembling tuberculosis.

3-Blastomycosis: Caused by Blastomyces dermatitidis.Like Histoplasma. Whene dissemination does occur, secondary sites include skin(70%),bone(30%), & the genitourinary tract(20%),where they manifest as ulcerated granulomas.Infections are more common in adult males than in females or children.

4-Paracoccidioidomycosis(South American blastomycosis): Caused by Paracoccidioides brasiliensis.The clinical presentation is much like(Histo-plasmosis & Blastomycosis) except that the most common secondary site of infection is the mucosa of the mouth and nose, where painful, destructive lesions may develop.90% of patients are mature males.

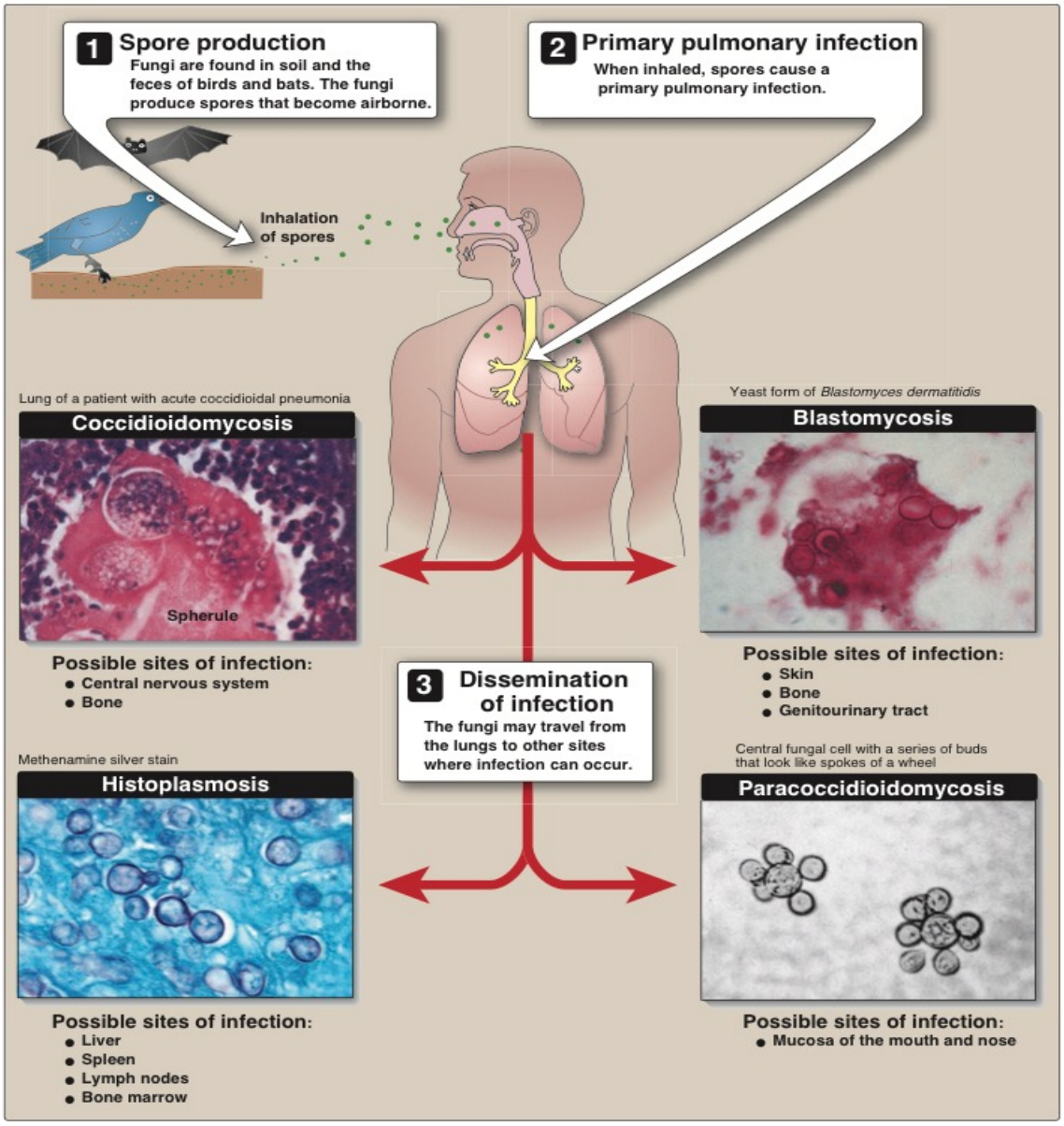
C.Laboratory identification:Histological examination of body fluids (sputum, pus, draining fistulas) for the presence of yeasts, hyphae,or conidia allows for rapid identification of the fungal etiological agent prior to the availability of culture results. The exoantigen test in which cell-free antigens produced by young mycelial colonies(or liquid culture) are detected by immunodiffusion assay. The exoantigen test can also be applied to urine specimens collected from patients suffering from histopla-smosis.PCR is a diagnostic method that detects specific fungal DNA seq.

D.Treatment: Usually with amphotericin B,sometimes in combination with flucytosine. Ketoconazole. fluconazole & intraconazole are also used, depending on the(infecting organism+stage+site)of the disease.

VI.Opportunistic Mycoses: Afflict debilitated or immunocompromi-sed individuals but are rare in healthy individuals.Fungal infections represent approximately 15% of all nosocomial (a result of treatment in a hospital)infections. The most commonly encountered today include :

A.Candidiasis(candidosis): Caused by Yeast candida albicans & other candida species(normal body flora in Skin, mouth, vagina, & intestines) infections occur when competing bacterial flora are eliminated. Candida infections have various manifestations, depending on the site & the degree of immunoincompetence of the patient. Systemic candidiasis is a potentially life-threatening infection that occurs in debilitated individuals, cancer patients, individuals on systemic corticosteroids, and patients treated with broad-spectrum antibiotics.It may involve the (GI)tract, kidneys, liver, & spleen. Both oral & vaginal infections are treated topically with nystatin or clotrimazole. Amphotericin B by itself or in combination with flucytosine is used in systemic disease.

B.Cryptococcosis: caused by the yeast Cryptococcus neoformans.The organism is especially abundant in soil containing bird(especially pigeon) droppings .The most common form of Cryptococcosisis a mild, subclinical lung infection. In immunocompromised patients, the infection often disse-mintes to the brain and meninges,with fatal consequences.In AIDS patients Cryptococcosis is the 2^{nd} most common fungal infection (after candidiasis)
& is potentially the most serious. The antifungal drugs used to treat crypto-coccosis are amphotericin B and flucytosine.



C. Aspergillosis: Caused by several species of the genus Aspergillus but primarily by Aspergillus fumigatus. They reside in dust soil ,& decom-posing organic matter.In fact, hospital outbreaks affecting neutropenic (with decreased neutrophils in their blood) patients. Aspergillosis manifests itself in several forms, depending in part on the patient's immunologic status.1.Acute aspergillosis infections: The most severe,& often fatal,form of aspergillosis is acute invasive infection of the lung, from which the infection can be disseminated to the brain ,GIT, and other organs. Although the lung is the commonest primary site of infection, the eye , ear, nasal sinuses, and skin can also be primary sites.2.Diagnosis and treatment:Definitive diagnosis is by detection of hyphal masses & isolation of the organism from clinical samples. Treatment of Aspergillus infections is typically by amphotericin B & surgical removal of fungal masses or infected tissue.

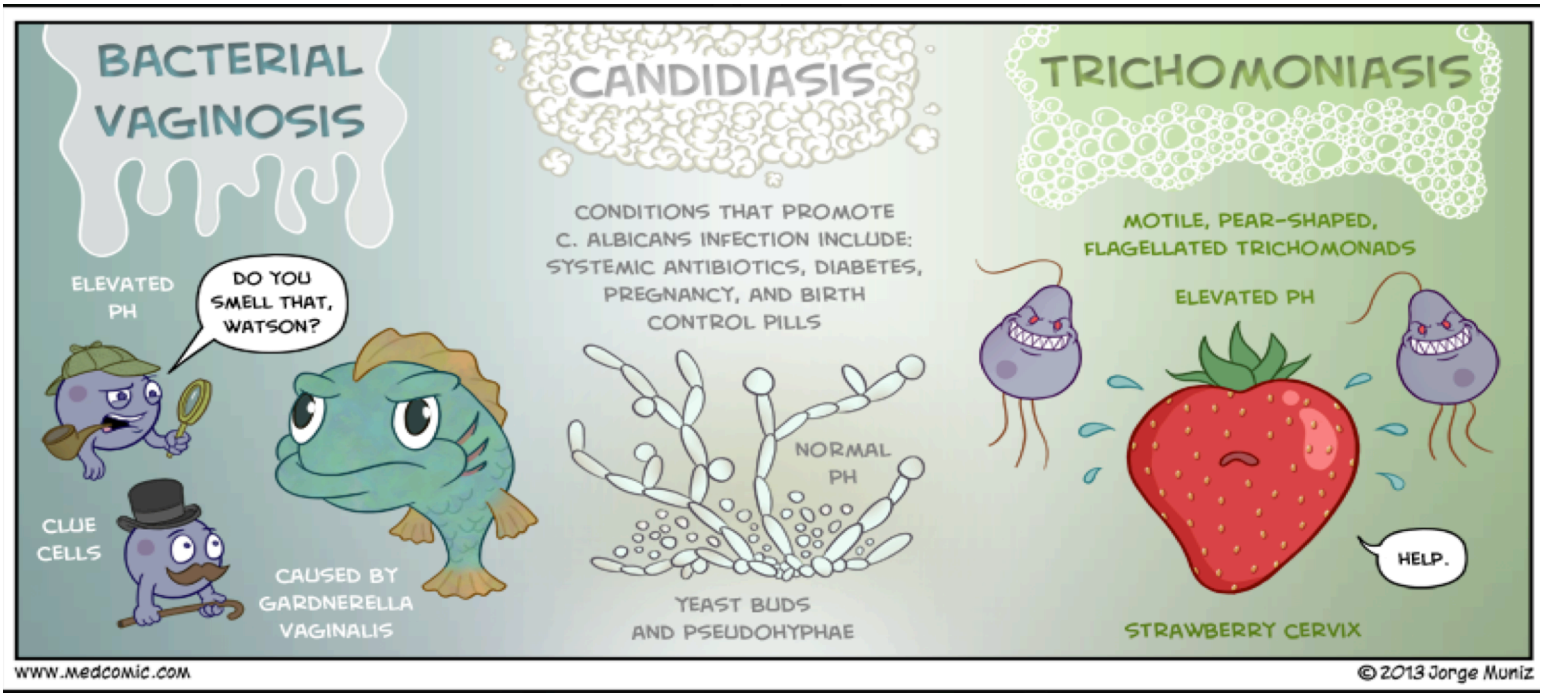
D.Mucormycosis: Caused most often by Rhizopus oryzae(R.arrhizus), & less often by other members of the order Mucorales(Absidia corymbifera & Rhizomucor pusillus). Mucor infections are almost entirely restricted to individuals with predisposing condition(burns, leukemias,DM). The most common form is rhinocerebral mucormycosis. Treatment is bsed on high-dose amphotericin B but must be accompanied, when possible, by surgical debridement of necrotic tissue.

E.Pneumocystis jiroveci: Caused by a yeast-like fungus called P.jiroveci(P.carinii).It's one of the most common opportunistic diseases of individuals infected with HIV-1(& almost 100%fatal if untreated).

1.Classification:P.jiroveci is a fungus related to the ascomycetous yeasts.

2.Pathology:It's not transmitted from person to person. Instead, develop-pment of P.jiroveci in immunodeficient patients is thought to be by activation of preexisting dormant cells in the lungs .

3.Diagnosis and treatment: Diagnosis is based on microscopic examin-ation of biopsied lung tissue or washings. The most effective therapy is a combination of sulfamethoxazole & trimethoprim, which is also used pro-phylactically to prevent infection in AIDS patients.



CHAPTER 21

Protozoa

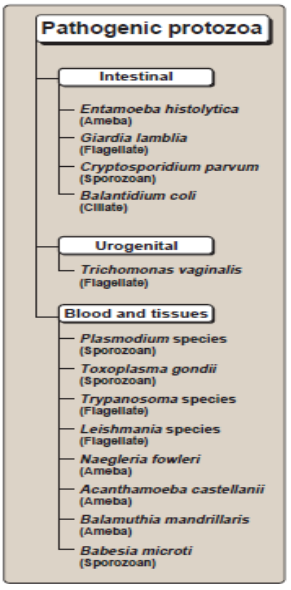


Figure 21.1
Clinically relevant protozoa, classified according to site of infection.

I.Overview: Protozoa are a diverse group of unicellular, eukaryotic organisms. Repr-oduction is generally by mitotic binary fission, although in some protozoal species, sexual(meiotic) reproduction. Only a few of protozoan species are pathogenic for hu-mans.These pathogens are of two general kinds: those that parasitize the intestinal & urogenital tracts & those that parasitize blood cells & tissues. Protozoal diseases are less easily treated because many antiprotozoal drugs are toxic to the human host

II.Classification of clinically important protozoa:The Pathogenic protozoa common features :1-Have both a dormant, immotile cyst stage.2-Actively feeding & reproducing, vegetative(trophozoite) stage. The clinically relevant protozoa are divided into four groups:

III. Intestinal Protozoal infections:

Name	Movement	Feed
A.Amebas	Extending cytoplasmic projections (pseudopodia).	By engulfing food particles with their pseudopodia.
B.Flagellates	Rotating whip-like flagella.	Ingest food particles through an oral groove called a cytostome.
C.Ciliates	Synchronous beating of hair-like cilia.	Have cytostomes that pass food particles through a cytopharynx & finally into vacuoles (digestion). (only Balantidium coli is pathogenic)
D.Sporozoa	Generally have non-motile adult forms.	

Name	Site of infection	Severity & Secondary consequences	Treatment
A.Amebic dysentery (Entamoeba histolytica)	Small intestine (ingested cysts) then pass to colon.	1-Inducing ulceration. 2-Spread to the liver(cause bscesses) *asymptomatic	1-Mild cases= iodoquinol. 2-Sever= metronidazole + chloroquine.
B.Giardiasis(Giardia lamblia)	Ingested cysts form trophozoites in the	*Often clinically mild, & some massive infection	Metronidazole

	duodenum	may damage the duodenal mucosa.	
C.Cryptosporidiosis (Cryptosporidium species)	Inhabits the epithelial cells of the villi of the lower small intestine.	*Asymptomatic to mild cases are common.	1.Normal=none 2.Immunocomprom-mised=Paromomycin.
D.Balantidiasis (Balantidium coli).	The ciliate protozoon B.coli causes dysentery by infecting the large intestine	1.Colonic ulcers(may perforate =>peritonitis) *Asymptomatic carriage to abdomi-nal discomfort & mild diarrhea to acute dysentery+blood+pus in stool.	Tetracyclines or Metronidizole.

IV.Urogenital tract infection: Trichomoniasis is caused by Trichomonas vaginalis. And it's the most common protozoal urogenital tract infection of human. In females, it causes inflammation of the mucosal tissue of the vagina, vulva, & cervix, accompany-ied by a copious, yellowish, malodorous discharge. Less commonly, it infects the male urethra, prostate, & seminal vesicles, producing a white discharge. The disease is largely sexually transmitted, & both (or all) sexual partners should be treated. Dia-gnosis is by detection of motile trophozoites in vaginal or urethral secretions. Labor-atory culture can be used to obtain observable organisms. Effective treatment is afforded by metronidazole.

V.Blood and tissue protozoal infections:

A.Malaria(Plasmodium falciparum& other species)	
Cause	by one of five species of the protozoal genus, Plasmodium, P.falciparum, P.vivax.
Transmition	The bite of a female Anopheles mosquito or by an infected, blood-contaminated, needle.
Cycle	Sporozoans reproduce asexually in human cells by (schizogony تكاثر انشطاري)in which multiple nuclear divisions are followed by envelopment of the nuclei by cell walls producing merozoites. These in turn , become trophozoites. Sexual reproduction occurs in the mosquito, where new spores are formed.
1-Pathology & clinical significance:	Plasmodium sporozoites are injected into the bloodstream ,where they rapidly migrate ti the liver. Upon release, the merozoites invade RBCs, using hemoglobin as nutrition. A predictable consequence of RBC lysis is anemia . P.falciparum is the most dangerous plasmodial species. It can cause a rapidly fulminating disease, characterized by persistent high fever and orthostatic hypotension. P.vivax, & P. vale they invade either young or old red cells, but not both. P.falciparum, which invades cells of all ages

2-Diagnosis and treatment :	*Thick blood smears stained with Giemsa stain provide the most sensitive visual test. Thin blood smears,are used to determine the species involved. Serologic tests are for diagnosis of acute disease. *Treatment is determined by the species, because P.falciparum has no exoerythrocytic phase, it needs only to be treated with quinine, artemisin, mefloquine or doxycycline. For ovale or vivax infections, after treatment with chloroquine, a two-week course of primaquine is necessary to achieve a 'radical cure' by eliminating exoerythrocytic organisms that persist in the liver.

B.Toxoplasmosis (Toxoplasma gondii): is an intracellular sporozon.	
Host	All vertebrate species (definitive host is the cat)
Infection	Accidental ingestion of oocysts present in cat feces ,eating raw meat ,congenitally from infected mother
1-Pathology & clinical significance:	There are 2 kinds found in human infections: 1.Rapidly growing tachyzoites(tachy=rapid)that are seen in body fluids in early, acute infections, They directly destroy cells(parenchymal + reticuloendothelial). 2.Slowly growing bradyzoites(brady=slow) that are contained in cysts in (muscle +brain tissue +eye). They cause local inflammation +blockage of blood vessels & necrosis.*Normal human hosts= asympto-matic. *Immunocompromised= sever. *Congenital= sever (stillbirths,brain lesions, and hydrocephaly)
2-Diagnosis, treatment :	Serologic tests to identify toxoplasma, include tests for Toxoplasma-specific immunoglobulin(Ig) G+ IgM
	Antifolate drug pyrimethamine, given in combination with sulfadiazine (or clindamycin).

C.Trypanosomiasis (virious trypanosome species): Refers to two chronic,(fatal) diseases (Figure21.11).

African sleeping sickness	American trypanosomiasis(Chagas disease)
1.Pathology & clinical significance:	
Caused by	Trypanosoma brucei gambiense (or rhodesiense)	Trypanosoma cruzi
Transmitted	By the bite of the tsetse fly.	Transmitted by insect feces contaminating the eye or a break in the skin.
Symptoms	Inflammation of the brain & spinal cord mediated by released toxins=> lethargy , continuous sleep & death.	Granulomatos lesion at the site of entry-> acute disease (fever & hepatosplnomegaly). Chronic infection (cardiomyopathy, megacolon)
2.Diagnosis and treatment:	
Diagnosis	African trypanosomiasis is made Primarily by detection of motile trypanosomes in giemsastained smears of body fluids.	
Treatment	Suramin or pentamidine.	Nifurtimox

D.Leishmaniasis (various leishmanial species): a group of infections caused by the flagellate protozoa of the genus Leishmania. Transmission to humans is by the bite of the female sandfly of the genus Phlebotomus or Lutzomyia.			
3 **clinical types :**	1.Cutaneous	2.Mucocutaneous	3.Visceral leishmaniasis
Local name	oriental sore	Espundia	Kala-azar
Cause	Leishmania tropica	Leishmania viannia brasiliensis	Leishmania donovani
Mechanism and Symptoms	Ulcerating single or multiple skin sores .	Attacks tissue at the mucosal-dermal junctions of the nose & mouth (multiple lesions)	Initially infects macrophages,which ,in turn, migrate to the spleen, liver, & bone marrow.*intermittent fever and weight loss, jaundice.
4.Diagnosis and treatment:			
***Examination of Giemsa-stained tissue & fluid samples for the nonflagellated form (amastigote).**			
From tissue samples taken from the edges of lesions or lymph node aspirates.			Liver ,spleen ,bone marrow biopsy
Treatment is difficult (available drugs considerable toxicity and high failure rates). Pentavalent antimonials are the conventional therapy.			

E.Amebic encephalitis (Naegleria fowleri, Acanthamoeba castellanii, and Balamuthia mandrillaris): Naegleria fowleri can cause primary amebic meningoe-ncephalitis (PAM) in immunocompetent individuals. The amebaexists in one of three morphological forms: flagellate, trophozoite, or cyst. The trophozoite (the infectious form found in fresh water) enters via the nasal cavity , generally infecting swimming children. From the nasal passages, the ameba directly invades the brain by way of the cribriform plate. Symptoms initially include headache, fever, and nausea. More than 95% of cases are fatal. B. Acanthamoeba cause granulomatous amebic enceph-alitis (GAE). Also cause cutaneous acanthamoebiasis, immunocompromised individ-uals. Acanthamoeba keratitis is an infection of the cornea. The source of the ameba is the contact lens solution. Balamuthia mandrillaris is causing encephalitis(BAE).

F.Babesiosis (Babesia microti) : is a protozoan.	
Transmitted	by the bite of an Ixodes tick
The reservoirs are	Small mammals & deer.
Mechanism and Symptoms	*Infects RBCs in the human accidental host, causing RBC lysis.* Are related to loss of RBCs (anemia).
Diagnosis	Babesia species generate ring-like trophozoites within erythrocytes.

CHAPTER 22

Helminths

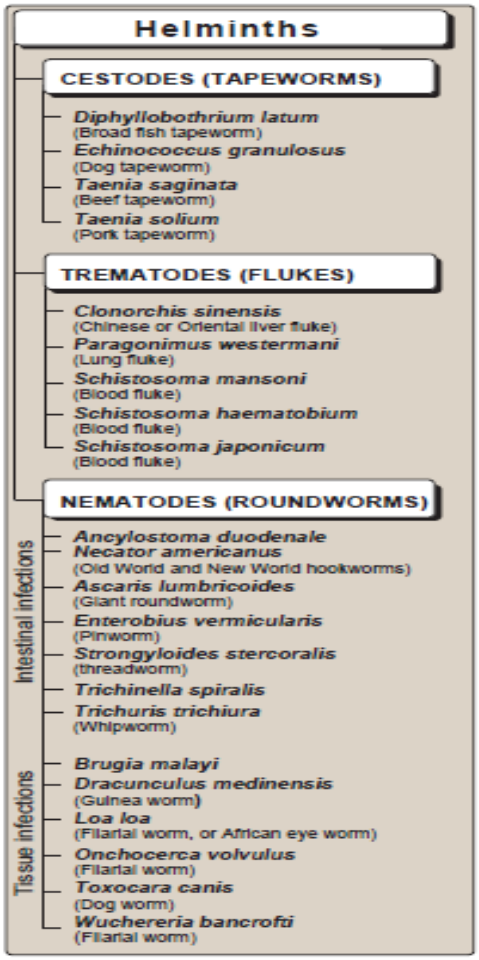


Figure 22.1
Clinically important helminths.

Overview: Helminths are worms, some of which are parasitic to humans. These parasites belong to one of three groups (Figure 22.1):

II.Cestodes : (tapeworms) are ribbon-like, segmented worms that are primarily intestinal parasites. They absorb soluble nutrients directly through their cuticles (lack a digestive system) Cause clinical injury by sequestering the host's nutrients; by excreting toxic waste => mechanical blockage of the intestine. The ant. End of the worm consists of a scolex , a bulbous structure with hooks & suckers that functions to attach the worm to the intestinal wall .Each proglottid (many segments) has a complete set of sexual organs(generate fertilized eggs) . Characteristics of infections (Figure 22.3).

III.Trematodes(flukes): are small ,flat, leaf-like worms. Infest various organs of the human host. All parasitic trematodes use freshwater snails as an intermediate host.

A.Hermaphroditic flukes: Developmental events in the life cycle of a typical fluke begin when the adult fluke produces eggs in the human (the definitive host). The eggs are then excreted into the environment. The first larval stage (miracidium) develops inside the eggs .These larvae seek out & infect suitable snail species, which are the first intermediate host. In the snail, asexual reproduction occurs. Large numbers of the final larval stage, called cercariae, which leave the snail & seek out second intermediate host (a fish or crustacean).

Transmission to humans varies
Ingestion of larvae in raw or undercooked pork, beef , or fish; ingestion of helminth eggs in feces, & by insect bites or direct skin penetration.

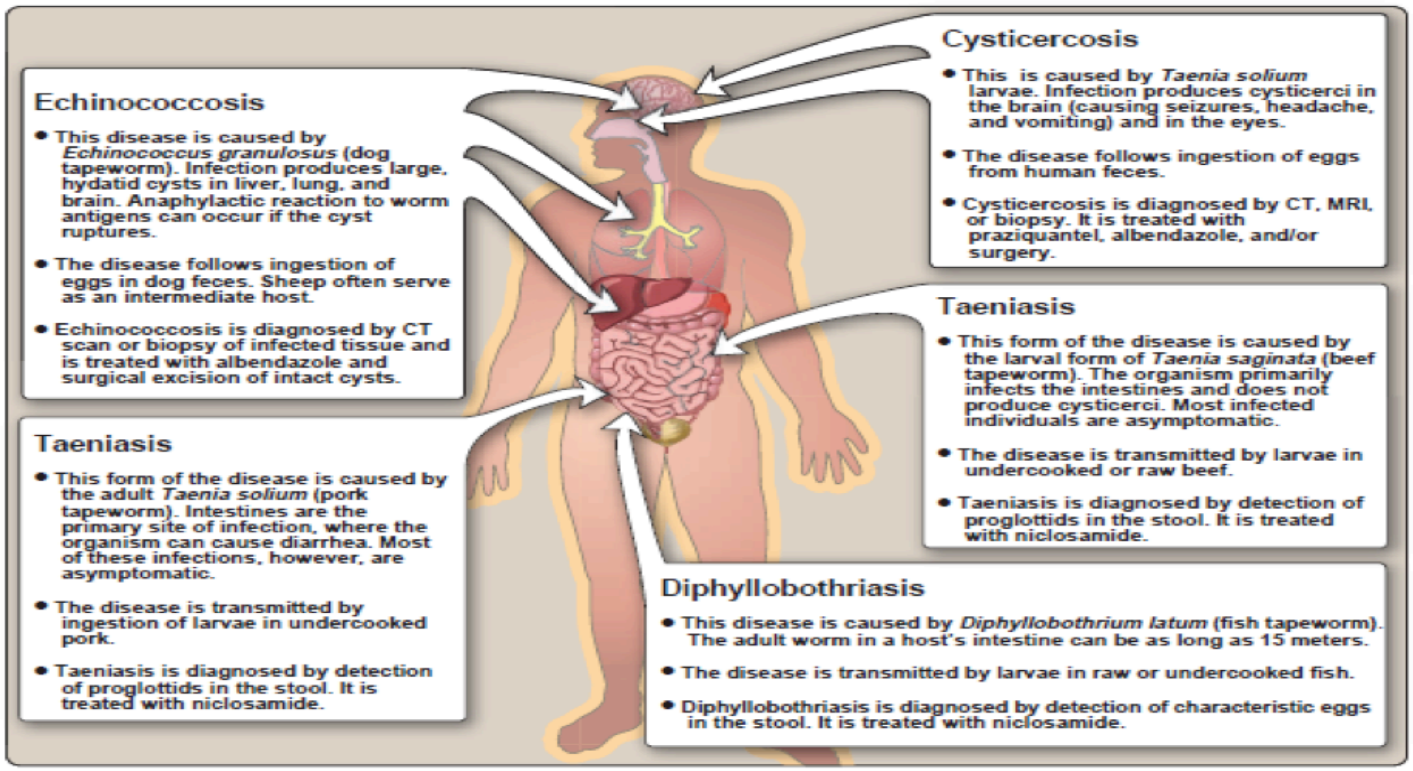
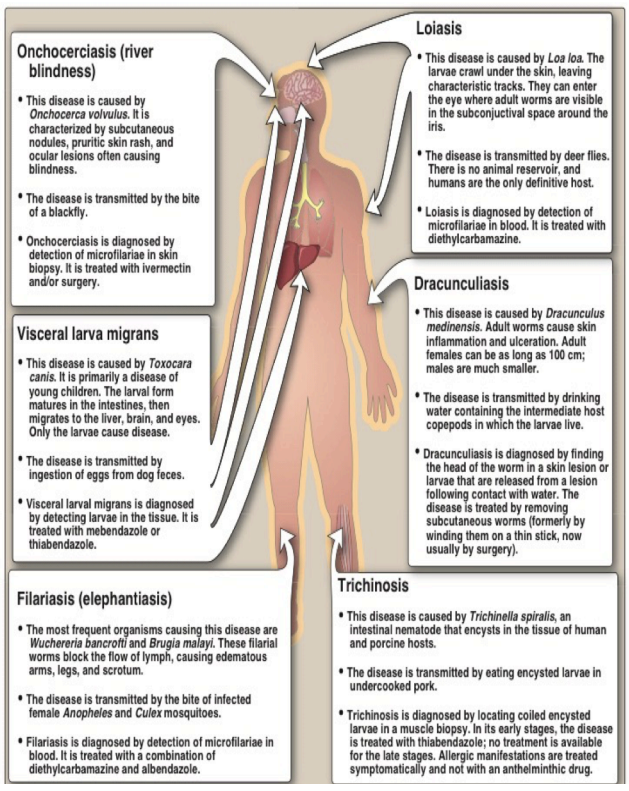
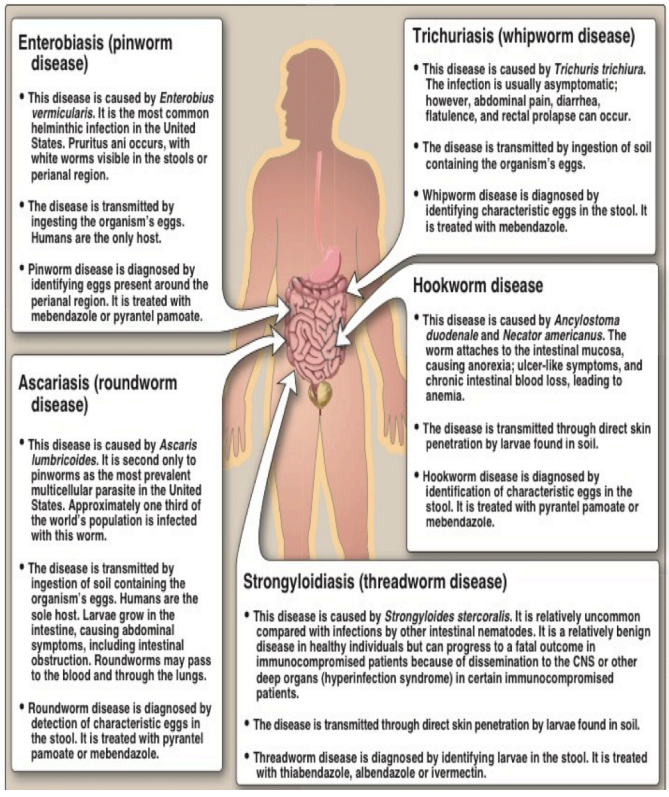


Figure 22.3
Characteristics and therapy for commonly encountered cestode infections. CT = computed tomography; MRI = magnetic resonance imaging.





Chapter 23

Introduction to the viruses

Overview: A virus is an infectious agent that is minimally constructed of two components:

1) **a genome consisting of RNA or DNA**
2) **a protein-containing structure (capsid)**

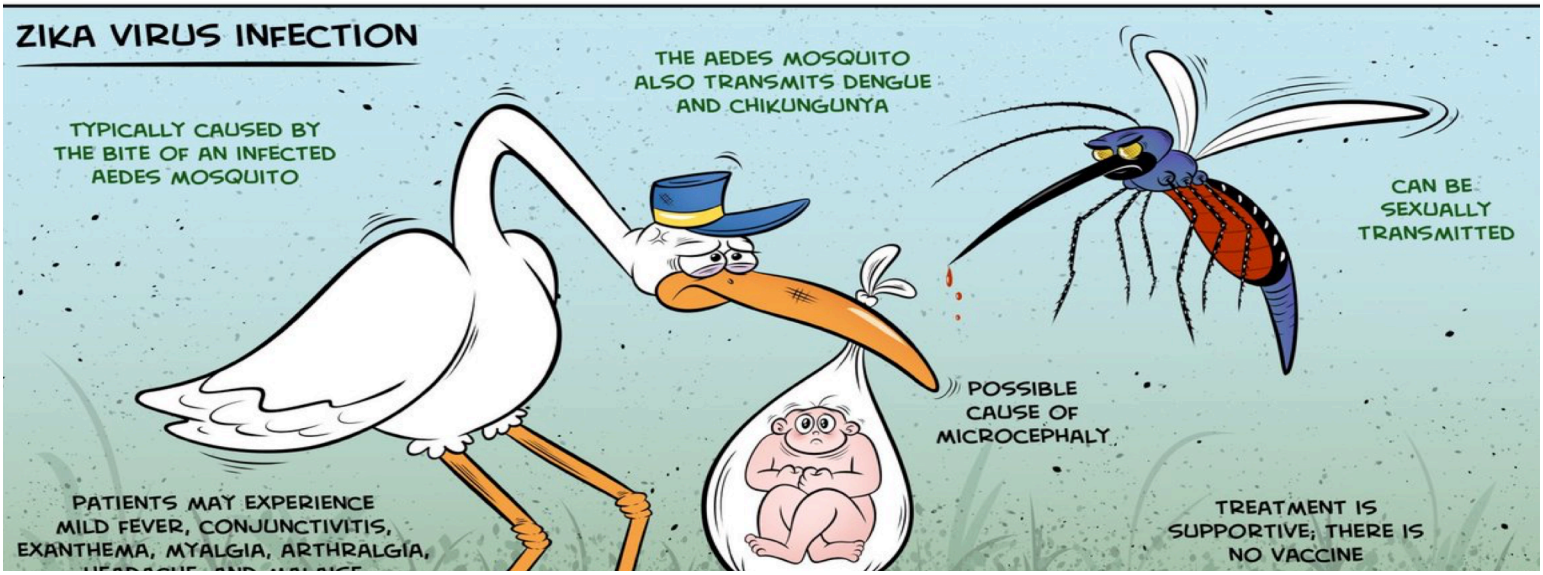
virion:
A complete virus particle combining these structural elements plus a lipid bilayer
a virion can be envisioned as a deliverysystem that surrounds a nucleic acid payload.

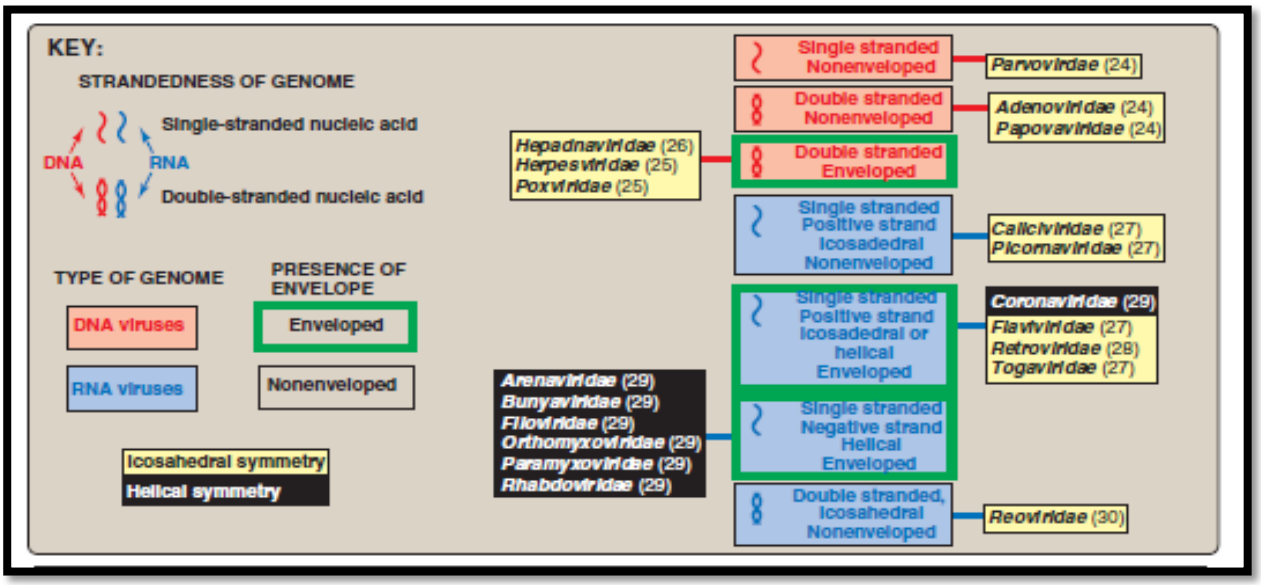
CHARACTERISTICS USED TO DEFINE VIRUS FAMILIES, GENERA, AND SPECIES :
Viruses are divided based on:

- **type and structure of the viral nucleic acid.**
- **presence or absence of a lipid envelope.**
- **the strategy used in its replication.**
- **type of symmetry of the virus capsid (helical versus icosahedral)**

Genome : The type of nucleic acid found in the virus particle is perhaps the most fundamental and straightforward of viral properties.

Capsid symmetry: The protein shell enclosing the genome is, for most virus families, found in either of two geometric configurations





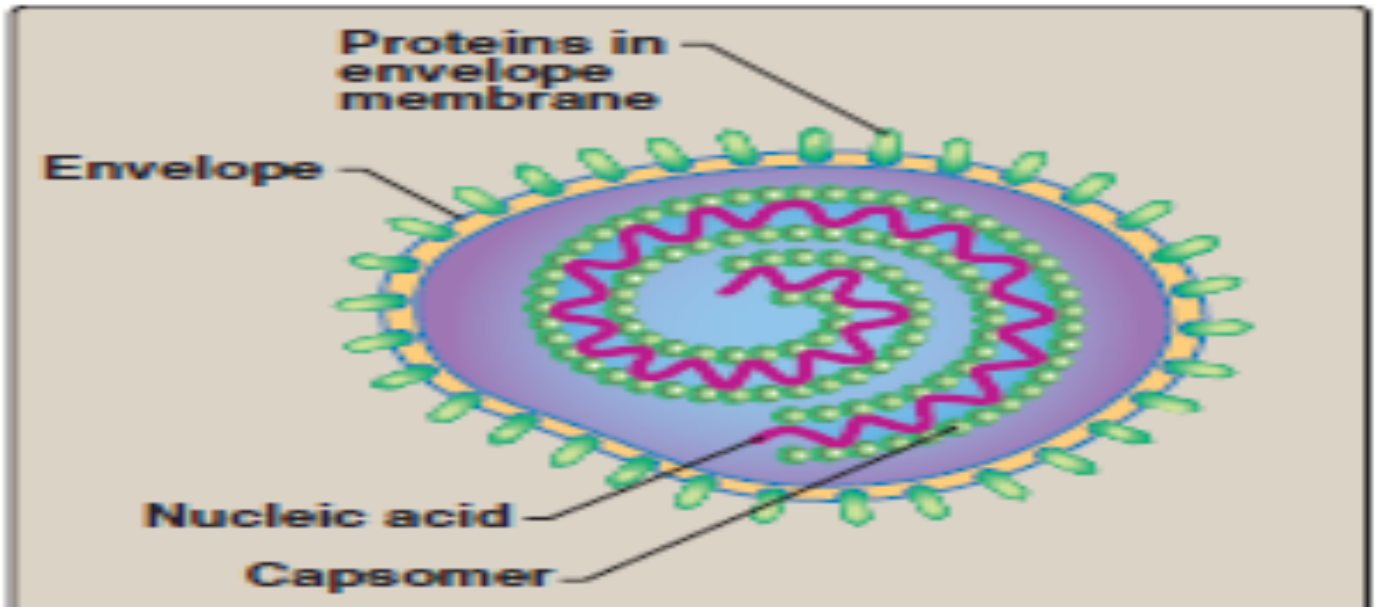
The figure is showing viral families classified according to type of genome, capsid symmetry, and presence or absence of an envelope. RNA is shown in blue, DNA in red, and viral envelope in green.

Envelope

An important structural feature used in defining a viral family is the presence or absence of a lipid-containing membrane surrounding the nucleocapsid.

VIRAL REPLICATION: THE ONE-STEP GROWTH CURVE :

The one-step growth curve is a representation of the overall change, with time, in the amount of infectious virus in a single cell that has been infected by a single virus particle. The one-step growth curve begins with the eclipse period, which is followed by aperiod of exponential growth

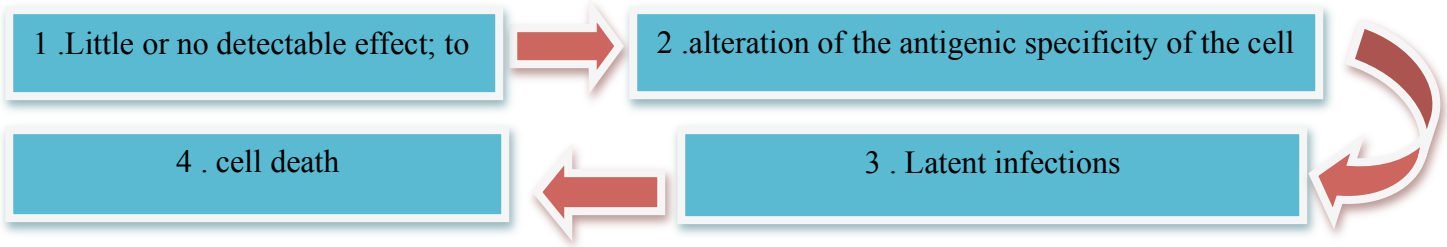


STEPS IN THE REPLICATION CYCLES OF VIRUSES: Beginning with virus attachment to the host cell and leading to penetration and uncoating of the viral genome.

1. **Adsorption**: The initial attachment of a virus particle to a host cell.
2. **Penetration** : The passage of the virion from the surface of the cell across the cell membrane and into the cytoplasm.
3. **Uncoating**: The stepwise process of disassembly of the virion that enables the expression of the viral genes that carry out replication.
4. **Mechanisms of DNA virus genome replication**: Each virus family differs in significant ways from all others in terms of the details of the macromolecular events comprising the replication cycle.
5. **Mechanisms of RNA virus genome replication:** Viruses with RNA genomes must overcome two specific problems that arise from the need to replicate the viral genome and to produce a number of viral proteins in eukaryotic host cell.
6. **Assembly and release of progeny viruses**: Assembly of nucleocapsids generally takes place in the host cell compartment where the viral nucleic acid replication occurs. It also have a :
   Naked viruses : In naked (unenveloped) viruses, the virion is complete at this point.
   Enveloped viruses: In enveloped viruses, virus-specific glycoproteins are synthesized and transported to the host cell membrane.

7. **Effects of viral infection on the host cell :**

- The response of a host cell to infection by a virus ranges from :



In summary, all viruses:
• are small;
• contain only one species of nucleic acid, either DNA or RNA;
• attach to their host cell with a specific receptor-binding protein; and
• express the information contained in the viral genome
(DNA or RNA) using the cellular machinery of the host cell.

CHAPTER 24
Non-enveloped DNA Viruses

I. **OVERVIEW:** The DNA viruses discussed in this chapter share the properties of lacking an envelope and having relatively simple structures and genome organization.

II. **INTRODUCTION TO THE PAPOVAVIRDAE:** Papovaviruses are nonenveloped (naked); have icosahedral nucleocapsids; and contain supercoiled, double-stranded, circular DNA.

III. **PAPOVAVIRIDAE: SUBFAMILY PAPILLOMAVIRINAE:** All papillomaviruses induce hyperplastic epithelial lesions in their host species. Over 150 types of human papillomaviruses (HPVs) are now recognized, based on differences in the DNA sequences of certain wellcharacterized virus genes.

IV. **PAPOVAVIRIDAE: SUBFAMILY POLYOMAVIRINAE:** All members of this virus subfamily have the capacity to transform normal cells in culture and to induce tumors in species other than those in which they are normally found in nature.

V. **ADENOVIRIDAE:**

Adenoviruses are nonenveloped, icosahedral viruses containing double-stranded linear DNA**.**

VI. **PAPOVAVIRIDAE: SUBFAMILY POLYOMAVIRINAE:** All members of this virus subfamily have the capacity to transform normal cells in culture and to induce tumors in species other than those in which they are normally found in nature.

- **Epidemiology and pathogenesis:** The human polyomaviruses BKV and JCV are transmitted by droplets from the upper respiratory tract of infected persons and, possibly, through contact with their urine.
- **Clinical significance:** Immune compromise of various types can be associated with the development of PML, so named because the lesions are restricted to white matter. PML, thought to be caused by reactivated JCV that has entered the central nervous system via the blood, occurs as a complication of a number of lymphoproliferative disorders and chronic diseases that affect immune competence.
- **Laboratory identification**: Because most people have antibodies to these viruses, serologic techniques are not generally useful in the diagnosis of acute infections.
- **Treatment and prevention**: No successful, specific, antiviral therapy is available. Because polyomavirus infection is nearly universal and asymptomatic.

V. ADENOVIRIDAE: Adenoviruses are nonenveloped, icosahedral viruses containing double-stranded linear DNA. They commonly cause diseases such as respiratory tract infections, gastroenteritis, and conjunctivitis.

- **Epidemiology and pathogenesis:** The site of the clinical syndrome caused by an adenovirus infection is generally related to the mode of virus transmission.
- **Structure and replication**: The adenovirus capsid is composed of hexon capsomers making up the triangular faces of the icosahedron, with a penton capsomer at each of the vertices.
- **Clinical significance**: Adenoviruses all replicate well in epithelial cells. The observed disease symptoms are related primarily to the killing of these cells, and systemic infections are rare. For example: respiratory tract diseases and ocular diseases.
- **Laboratory identification**: Isolation of virus for identification is not done on a routine basis but may be desirable in cases of epidemic disease or nosocomial outbreak, especially in the nursery.
- **Treatment and prevention**: No antiviral agents are currently available for treating adenovirus infections. Prevention of epidemic respiratory disease by immunization has been used only for protection of the military population.

VI. PARVOVIRIDAE: Parvoviruses are the smallest of the DNA viruses. They are nonenveloped and icosahedral, with single-stranded, linear DNA.

- **Epidemiology and pathogenesis**: Transmission of parvoviruses is by the respiratory route. A hightitered viremia lasting a few days follows about 1 week after infection, during which time virus is also present in throat secretions.
- **Clinical significance**: The single human pathogen in this family is the autonomous parvovirus, B19. The spectrum of illnesses caused by this virus is related to its unique tropism for cycling erythroid progenitor cells. For example: Erythema infectiosum , Birth defects.
- **Laboratory identification:** Laboratory identification of B19 infection is not routinely done. The large amount of virus present during the viremic (usually asymptomatic) phase permits detection of viral proteins by immunologic methods or of viral DNA by various amplification techniques.
- **Treatment and prevention** No antiviral agent or vaccine is available for treating human B19 infections.

CHAPTER 25

Enveloped DNA Viruses

Overview

In this chapter we will discuss the two of the three enveloped DNA viruses :Herpesviridae&Poxviridae.Genetically &structurally they are more complex than Nonenveloped DNA viruses. They are less need to host cell for cell–supplied functions and replication independent of the host cell.Herpesviridae&Poxviridae families includes important pathogens (Figure 25.1).

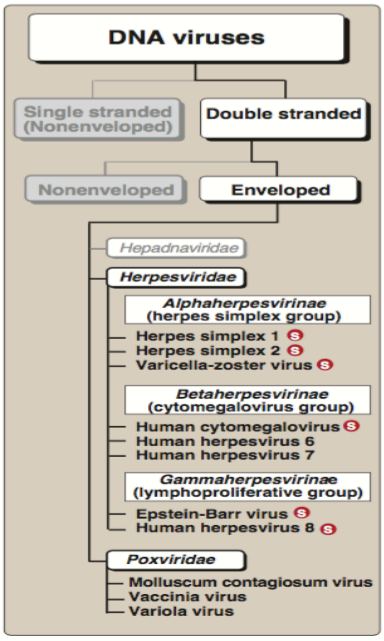


Figure 25.1
Classification of enveloped DNA viruses. S See p. 356 for summaries of these viruses.

HERPESVIRIDAE: STRUCTURE AND REPLICATION

There are 8 herpesvirus species, they enter in latent state waiting to be activated.

Structure of herpesviruses

It consist of an icosahedral capsid enveloped by the host membrane, between the envelope and the capsid lies protein materials without a clearly defined shape called Tegument (virus-encoded enzymes and transcription factors) witch initiate the infection. The genum is dsDNA (Figure 25.2).

Classification of herpesviruses

It divided into three subfamilies, based on biologic characteristics:

1. **Alphaherpesvirinae (herpes simplex virus group):**
   Have a rapid growth cycleand establish latent infections in nerve ganglia.e.g. (HSV-1, HSV-2, VZV)
2. **Betaherpesvirinae (cytomegalovirus group):**
   Have a slow replication cycle which form multinucleated, giant host cells. Established in lymphoreticular cells &glandular tissues.e.g. (HCMV, HHV-6,HHV-7).
3. **Gammaherpesvirinae (lymphoproliferative group):**
   Replicate in mucosal epithelium and establish latent infections. It proliferate & immortalize lymphoblastoid cells. e.g. (EBV, HHV-8).

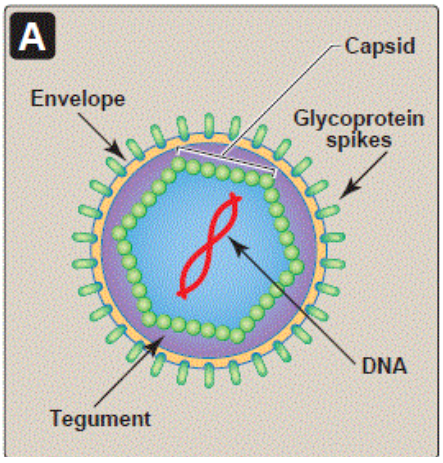


Figure 25.2

Replication of the herpesviruses (Figure 25.3)

Replicate in the nucleus. Regulated by cascade control (first set of genes is required for the second set).

1. **Virus adsorption and penetration:**
   The virus adsorbed by the receptors to the host cell. Then the envelop glycoproteins fuse with the cell membrane. The nucleocapsid& tegument will be release in the cytosol.One of the teguments (RNase) degrades all mRNAs, shutting protein synthesis.
2. **Viral DNA replication and nucleocapsid assembly:**
   Nucleocapsid transported to the pores on the nucleus, and release the viral DNA. Tegument activate cellular RNA polymerase to initiate transcription of the set of the viral genes to initiate another gene transcription.
3. **Viral envelope acquisition:**
   Newly synthesized envelopes assemble with the new nucleocapsid forming a complete virus, which transported by vacuole to the cel membrane. Envelop glycoprotein may cause fusion of near cells producing multinucleated giant cell. The end result cell death because most cellular synthetic pathways turned off.
4. **Latency:**
   Another way to infect by entering quietly, dormant state (latency) from whichthey can subsequently be reactivated.

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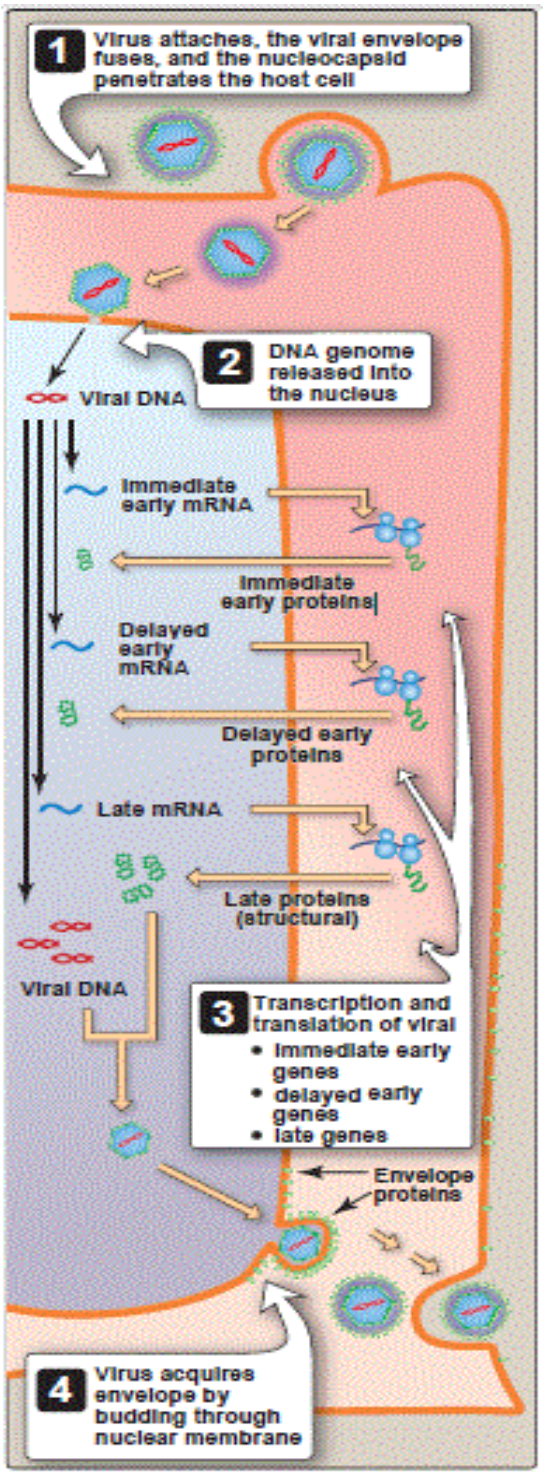


Figure 25.3

Herpes simplex virus, types 1 and 2

HSV-1 and HSV-2 are the only human herpesviruses that have a significant degree of nucleotide sequence identity.

Epidemiology and pathogenesis

transmission of both HSV types is by direct contact with viruscontainin secretions or with lesions on mucosal or cutaneous surfaces. Infections in the oropharyngeal region, caused by HSV-1, it transported by sliva & kissing & contaminated fingers. Infections in genetal tract caused by HSV-2, it transported by sexual intercourse & for newborns through birth canal.

Clinical significance

In general HSV-1 commonly found above the waist & HSV-2 below the waist. However HSV-1 can infect genital tract & HSV-2 can infect oropharyngeal region.

1. Primary infections of the upper body: (oropharyngeal region)
   gingivostomatitis in young children and pharyngitis or tonsillitis in adults. The lesions consist of vesicles and ulcers , accompanied with fever, malaise, myalgia. important site of infection is the eye, it can lead to blindness. If HSV infect the CNS, it can cause encephalitis.
2. Primary infections of the genital tract: (genital tract)
   The lesions are similar to those of the upper body with severity of the symptoms. In pregnant women with a primary genital HSV infection, the risk of infecting the newborn during birth is estimated to be 30 to 40 % (neonatal herpes).
3. Latency: A (Figure 25.6)
4. Reactivation: B (Figure 25.6)
   a. Herpes simplex virus type 1: The frequency of oropharyngeal symptomatic recurrences is variable (non, several ayear).
   b. Herpes simplex virus type 2: Reactivation of HSV-2 genital infections can occur with considerably greater frequency (monthly).

Laboratory identification

Direct detection of viral DNA by hybridization techniques complements these procedures and, after amplification of the
DNA by polymerase chain reaction, is considerably more sensitive than using of immunofluorescence or immunoperoxidase staining with antibodies.

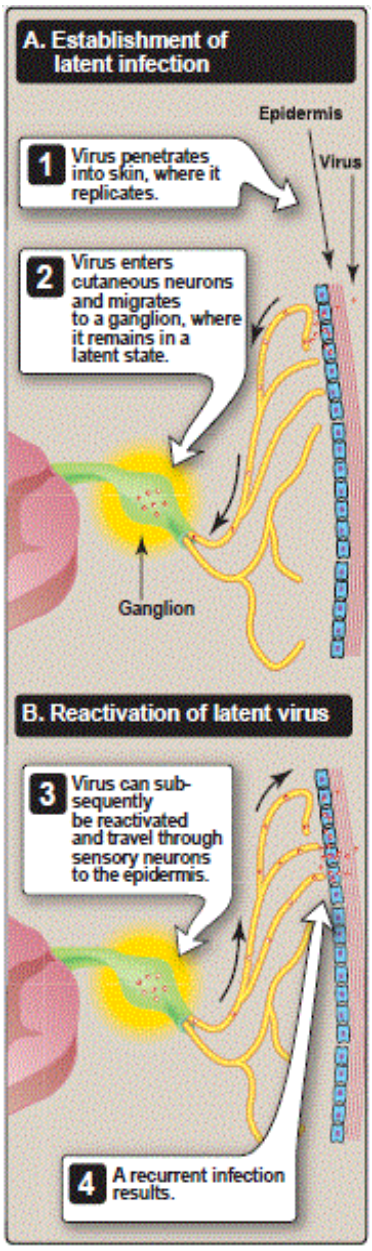


Figure 25.6
Primary and recurrent herpes simplex infections.

Treatment

The drug of choice for any primary HSV infection, acyclovir is especially important in treating herpes encephalitis, neonatal herpes, and disseminated infections in immunocompromised patients. Other drugs famciclovir and topical penciclovir. None of these drugs can cure a latent infection, but they can minimize asymptomatic viral shedding and recurrences of symptoms.

Prevention

Avoidance of contact with potential virus-shedding lesions and by safe sexual practice. In newborns, often it is hard to know if the mother infected (asymptomatic infection), when overt genital tract lesions are detected at the time of delivery, cesarean section is usually warranted

VARICELLA-ZOSTER VIRUS

VZV has biologic and genetic similarities to HSV and is classified with HSVs in the Alphaherpesvirinae subfamily.

Epidemiology and pathogenesis

VZV is the only herpesvirus that can be easily spread from person to person by casual contact.

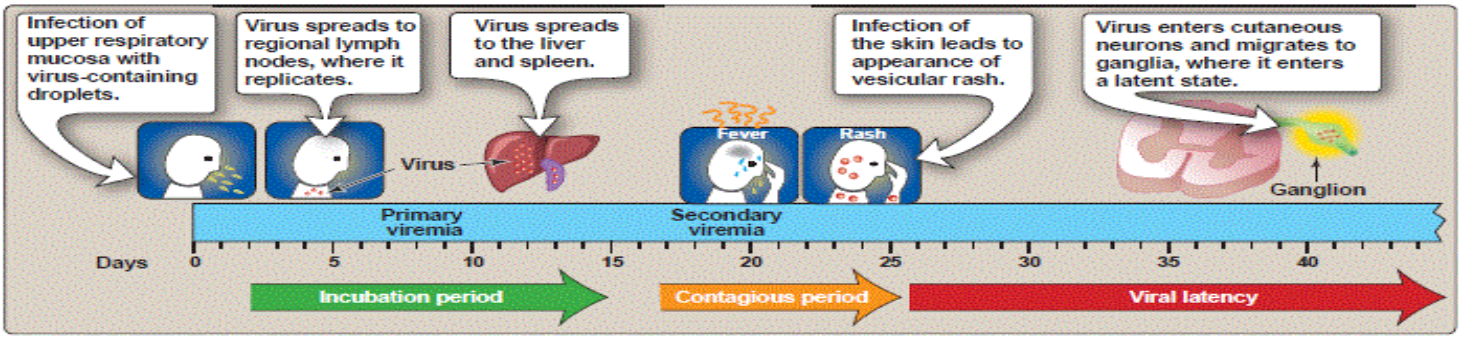


Figure 25.10
Time course of varicella (chickenpox) in children. In adults, the disease shows a longer time course and is more severe.

Clinical significance

Both can have severe complications in immunocompromised patients.

1. Primary infection (varicella, or chickenpox):
   Varicella is a more serious disease in both healthy and immunocompromised adults than it is in children. Varicella pneumonia is the most common of the serious complications, but fulminant hepatic failure and varicella encephalitis may also result. Fetal infection early in pregnancy is uncommon but can result in multiple developmental anomalies.
2. Reye syndrome:
   Reye syndrome, an acute encephalopathy accompanied by fatty liver, can sometimes follow VZV or influenza infections in children.
3. Recurrent infection (herpes zoster, or shingles):
   Herpes zoster results from reactivation of the latent virus, rather than from new, exogenous exposure. Reactivation occurs in up to 30 percent of individuals who have been infected at some point during their lifetime, and the likelihood increases with advancing age. The distribution of the clustered vesicular lesions is dermatomal (affecting the area of skin supplied by cutaneous branches from a single spinal nerve).

Laboratory identification It can be detected by reacting epithelial cells scraped from the base of vesicles with the immunofluorescence or immunoperoxidase staining or by doing in situ hybridization with VZV-specific DNA probes.

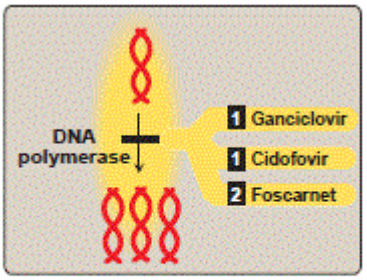


Figure 25.17
Drug therapy for cytomegalovirus.
1 Indicates first-line drugs;
2 indicates alternative drug.

Treatment

Famciclovir and valacyclovir (base analogs similar to acyclovir) have greater activity against VZV. (Figure 25.13)

Prevention

Certain people can be protected by administration of varicella zoster immunoglobulin (VariZIG). (infants, children, adults)

HUMAN CYTOMEGALOVIRUS

HCMV is a member of the Betaherpesvirinae subfamily and, as such, differs from HSV and VZV in several ways. Its replication cycle is significantly longer, and infected cells typically are greatly enlarged and multinucleated.

Epidemiology and pathogenesis

First infection commonly occurs in childhood. Most of people get the antibodies by adulthood.

1. **Transmission:**
   - Sexual means.
   - Organ transplant.
   - Blood transfusion.
   - Saliva, tears, urine.

2. **Latency and reactivation:**
   A distinctive feature of HCMV latency is the phenomenon of repeated episodes of asymptomatic virus shedding over prolonged periods.

Clinical significance

Usually it is subclinical. 8 % of infectious mononucleosis (IM) cases are caused by HCMV. Persistent fever, muscle pain, and lymphadenopathy are characteristic IM symptoms, as are elevated levels of abnormal lymphocytes and liver enzymes. HCMV distinguished by absence of the heterophile antibodies that characterize IM caused by EBV.

specific situations have greater clinical significance :

1. **Congenital infections:**
   HCMV is the most common intrauterine viral infection. Results of the infection range from varying degrees of damage to liver, spleen, blood-forming organs, and components of the nervous system to fetal death.

2. **Infections of immunosuppressed and immunodeficient patients:**
   Transplant recipients are multiply at risk from:
   - Present of HCMV in transplanted tissue.
   - Carried HMCV in leukocytes of the blood transfusion.
   - Reactivation of their own endogenous latent virus.

Destruction of GI tract tissue, hepatitis, and pneumonia are common, the latter being a major cause of death in bone marrow transplant recipients.

Laboratory identification

Serologic diagnosis using ELISA (or, enzyme-linked immunosorbent assay) techniques can distinguish primary from recurrent infection by demonstrating IgG seroconversion or the presence of HCMV-specific IgM.

Treatment and prevention

Treatment of HCMV infection is indicated primarily in immunocompromised patients (Figure 25.17). A vaccine for active immunization is not available.

HUMAN HERPESVIRUS TYPES 6 AND 7

Classified as members of the Betaherpesvirinae, have marked similarities to HCMV in biologic and genome characteristics.

Epidemiology and pathogenesis

Mostly it occurs during the first 3 years. Transported by oral secretions (saliva) because the viruses replicate in the oropharynx. It extends the range of cells that can be infected by HIV.(ايدز)

Clinical significance

HHV-6 infections resulting in disease are most common in infants and individuals who are immunocompromised.

1. **Primary infections:**
   Symptomatic roseola infantum (exanthema subitum) occurs in roughly 1/3 to 1/2 of infants with a primary HHV-6 infection. It is characterized by a high fever of 3 to 5 days' duration, after which a characteristic erythematous macular rash appears on the neck and trunk. HHV-7 infection has been shown to produce an identical clinical picture.
2. **Recurrent infections:**
   Following immunosuppression for organ transplantation or immunocompromise related to HIV infection, reactivation of latent HHV-6, frequently together with HCMV, has been associated with sometimes-fatal interstitial pneumonitis, fever, hepatitis, and encephalitis as well as with transplant rejection.

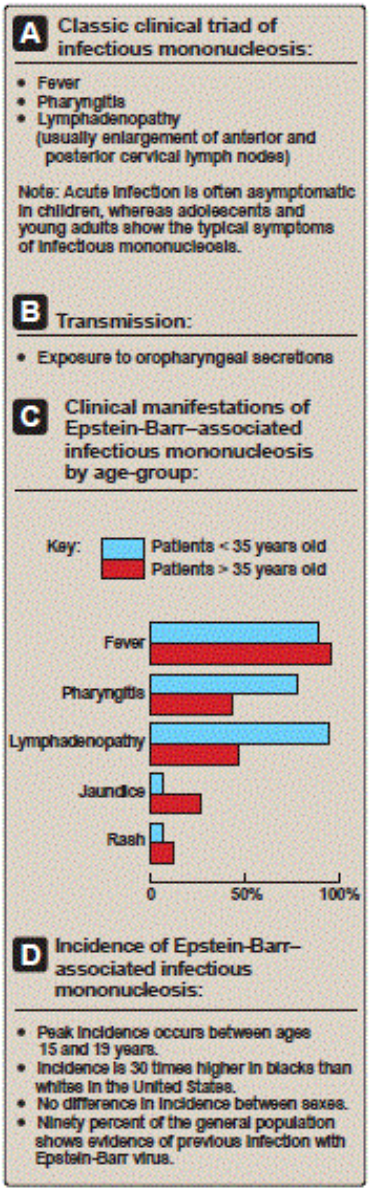


Figure 25.22
Characteristics of infectious mononucleosis.

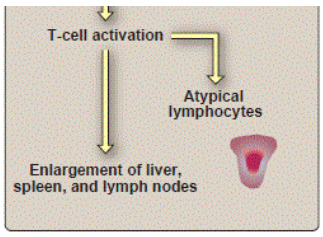


Figure 25.21
Pathogenesis of infectious mononucleosis caused by Epstein-Barr virus (EBV).

Laboratory identification

PCR (polymerase chain reaction) amplification has been used to demonstrate HHV-6 DNA in the CSF (cerebrospinal fluid) of patients with neurologic disease and in the serum of patients undergoing posttransplant reactivation of a latent infection.

Treatment and prevention

Because of its genetic relationship to HCMV, HHV-6 is generally inhibited by the same drugs (ganciclovir, cidofovir, and foscarnet). No vaccine is currently available for these viruses.

HUMAN HERPESVIRUS TYPE 8

HHV-8 infection appears not to occur as frequently as the other human herpesviruses in the normal, healthy population. Yet the virus genome and/or viral proteins have been detected in more than 90 percent of patients with KS, but in less than 1 percent of non-KS tissues. The primary method for detection of HHV-8 is PCR amplification.

EPSTEIN-BARR VIRUS

EBV is most commonly known as the causative agent of IM in young adults.

Epidemiology and pathogenesis

Most transmission of EBV occurs by intimate contact with saliva that contains virus during both primary infection and in repeated episodes of asymptomatic shedding (Figure 25.21).

Clinical significance

In patients who are immunodeficient or immunosuppressed, the lack of cell-mediated immune control increases the likelihood of lymphoproliferative disorders of various kinds.

1. **Infectious mononucleosis:**
   (Figure 25.22).
2. **EBV and malignancies:**
   - Burkitt lymphoma(BL):
     BL cells all contain one of three characteristic chromosome translocations. Malarial infection and HIV infection are known risk factors for development of BL.
   - Epstein-Barr–associated nasopharyngeal carcinoma(NPC):
     NPC differs from BL in that there is no characteristic chromosomal alteration, and the cells involved are epithelial in origin.
   - Epstein-Barr virus infections In immunocompromised and immunosuppressed patients:
     EBV alone appears to be sufficient for induction of B-cell lymphomas in immunocompromised patients, such as transplant recipients and individuals with AIDS, who cannot control the cell multiplication induced by the early proteins.

Laboratory identification:

The classic test for IM, the Paul-Bunnell test, is based upon the nonspecific elevation of all Igs, including heterophile antibodies that specifically agglutinate horse and sheep red blood cells, during polyclonal stimulation of B cells by EBV infection.

Treatment and prevention

No antiherpes drug can actively effect EBV. No vaccine for prevention of EBV infections is currently available.

Some properties of the common herpesvirus infections are summarized in (Figure 25.25).

VIRUS	VIRUS SUBFAMILY	CLINICAL MANIFESTATIONS OF PRIMARY INFECTION	CLINICAL MANIFESTATIONS OF RECURRENT INFECTION	SITE OF INITIAL INFECTION	SITE OF LATENCY
Herpes simplex-1	α	Keratoconjunctivitis, gingivostomatitis, pharyngitis, tonsilitis	Herpes labialis ("cold sores")	Mucoepithelial	Trigeminal sensory ganglia
Herpes simplex-2	α	Genital herpes, perinatal disseminated disease	Genital herpes	Mucoepithelial	Lumbar or sacral sensory ganglia
Varicella-zoster virus	α	Varicella ("chickenpox")	Herpes-Zoster ("shingles")	Mucoepithelial	Trigeminal and dorsal root ganglia
Cytomegalo-virus	β	Congenital infection (in utero), mono-nucleosis-like syndrome	Asymptomatic shedding of virus	Monocytes, lymphocytes, and epithelial cells	Monocytes, lymphocytes
Epstein-Barr virus	γ	Infectious mono-nucleosis, Burkitt lymphoma	Asymptomatic shedding of virus	Mucosal epithelium, B lymphocytes	B lymphocytes

Figure 25.25
Properties of common herpesvirus infections.

POXVIRIDAE It belong to a family of large, genetically complex viruses having no obvious symmetry. Members of this family are widely distributed in nature.

Structure and classification of the family

The genome is a single linear molecule of double-stranded DNA.

Replication of the poxviruses

Basic replication pattern for DNA viruses, with a few notable exceptions. the entire replication cycle takes place in the cytoplasm, the virus providing all of the enzymes (including a viral DNA-dependent RNA polymerase) necessary for DNA replication and gene expression.

Epidemiology and clinical significance

Stages of smallpox (Figure 25.26). smallpox is no longer a threat, the mutation of one of the animal poxviruses to a form more virulent for humans has continued to be of concern.

Laboratory identification

The unique cellular localization of poxvirus replication has enabled rapid diagnosis by observation of DNA-containing intracytoplasmic inclusion bodies in cells scraped from skin lesions.

Treatment and prevention

Although immunization with vaccinia is no longer done routinely, it is still carried out in certain groups, such as the military and laboratory workers. Although one of the safest vaccines in healthy recipients, individuals with eczema may develop a generalized vaccinia rash covering the surface of the body. Immunocompromised patients are likely to develop progressive vaccinia, which has a high mortality rate. Postvaccinal encephalitis, with a mortality of 40 percent, is a rare secondary hazard accompanying vaccination.

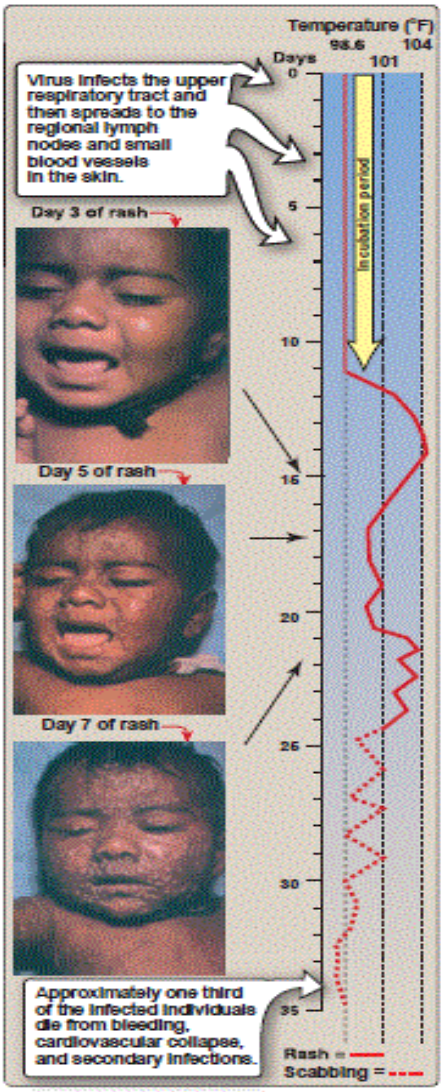


Figure 25.26
Time course of smallpox.

CHAPTER 26
Hepatitis B and Hepatitis D (Delta)

Overview

This chapter will discusses the defective agent that sometimes accompanies HBV during infections: the "delta agent," or hepatitis D virus (HDV). With the exception of HBV, hepatitis viruses thus far identified (hepatitis A, C, D, and E viruses) contain RNA and belong to several different families. Outcome of infection and mode of transmission, however, differ significantly from virus to virus.

HEPADNAVIRIDAE

Consists of hepatitis-causing viruses with DNA genomes.Each hepadnavirusproduces both acute and chronic, persistent infections, but HBV is the only member of this family that infects humans.

Structure and replication of hepatitis B virus

The HBV virion consists of an icosahedral nucleocapsid enclosed in an envelope (Figure 26.4).

1. Organization of the hepatitis B virus genome:
   Circular structure. It is a partly single-stranded,partly double-stranded, noncovalently closed, circular DNAmolecule (that is, one strand is longer than the other).(Figure 26.4)
2. Viral proteins:
   - The core protein [hepatitis B nucleocapsid core antigen (HBcAg)].
   - Envelope protein [a glycoprotein referred to as hepatitis B surfaceantigen (HBsAg)].
   - Multifunctional reverse transcriptase/DNApolymerase.
   - A nonstructural regulatory protein designated the "X protein".

Transmission

All body fluids of an infected individual. Therefore, blood, semen, saliva, and breastmilk, serve as sources of infection.

Pathogenesis

Hepatocytes are the primary cell type infected by HBV. The cause of hepatic cell destruction isthe cell-mediated immune response, which results in inflammation and necrosis. The cells involved are cytotoxic T cells, which react specifically with the fragments of nucleocapsid proteins (HBcAg and HBeAg).

Clinical significance: acute disease

Medically and in public health, not only as the cause of acute liver disease but also as the cause of chronic.

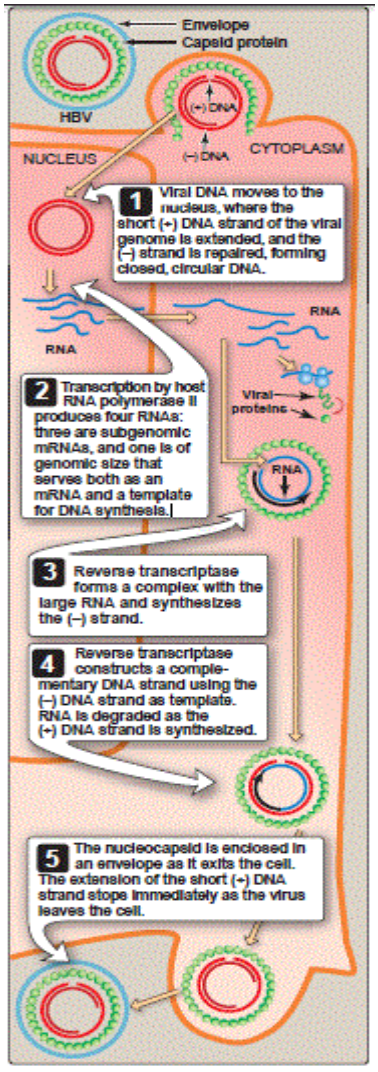
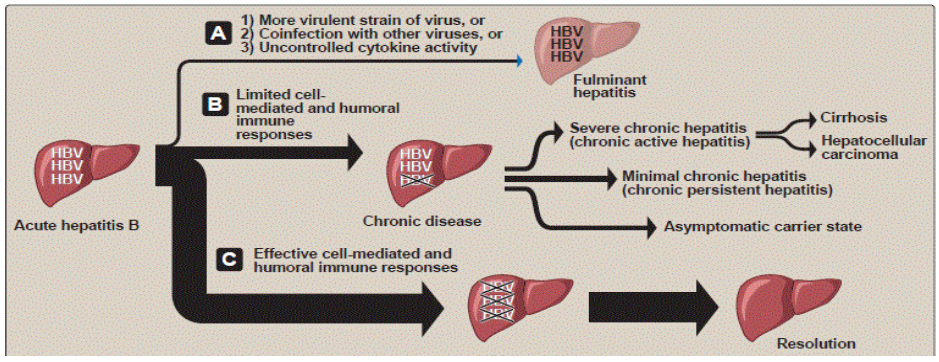


Figure 26.4
Replication of hepatitis B virus (HBV).



1. Phases in acute hepatitis B virus infections:
   - incubation period of between 45 and 120 days.
   - Pre-icteric (prejaundice) phase, days to week.
   - The acuteicteric phase, 1-2 monthes.
2. Monitoring the course of acute hepatitis B virus infection:
   the quantities ofvirions and virion components in the blood are so great that the timecourse of their appearance and clearance, along with that of theantibodies directed against them, serve as convenient markers ofthe stage of the disease.

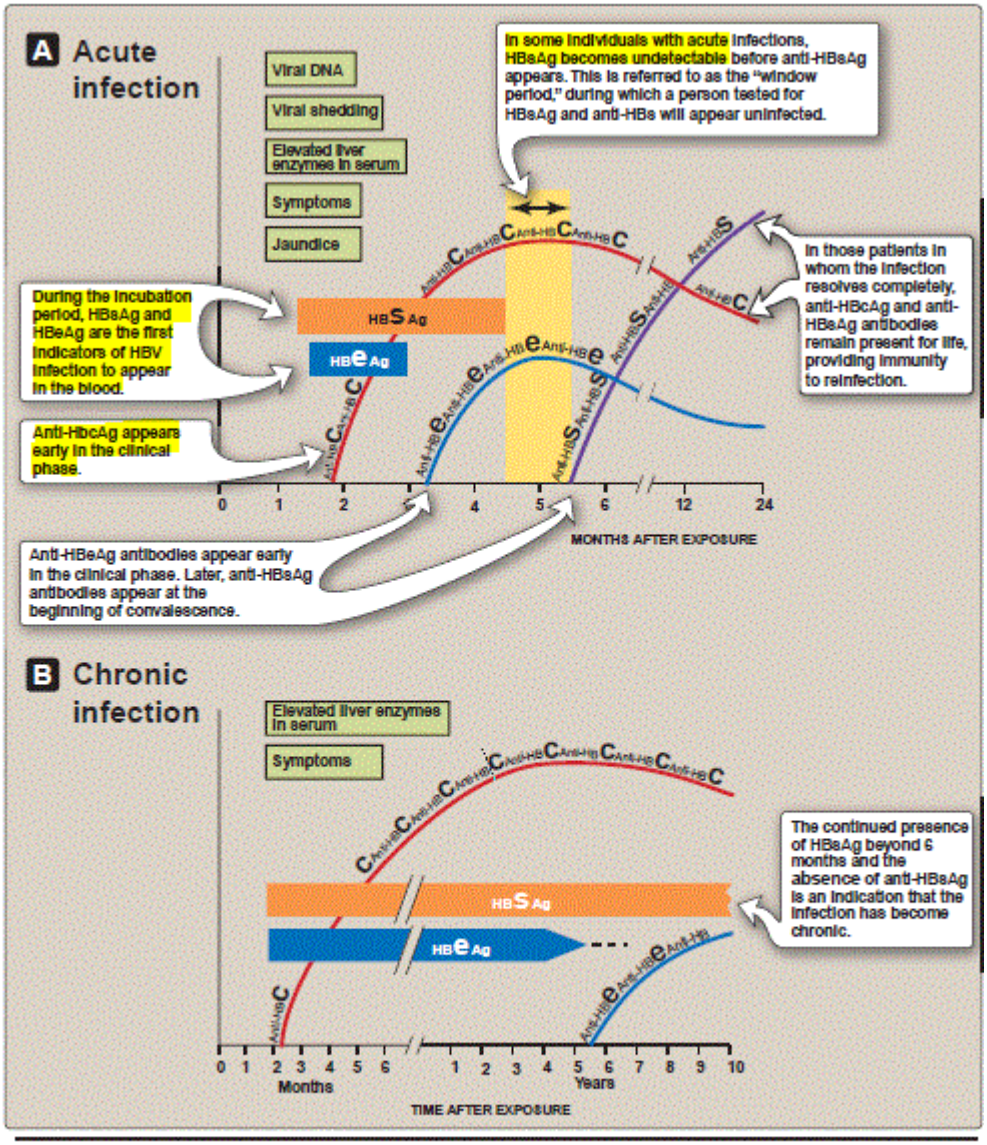


Figure 26.7
Typical course of hepatitis B virus infection. A. Acute infection. B. Chronic infection. HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBcAg = hepatitis B nucleocapsid core antigen; anti-HBsAg, anti-HBeAg, and anti-HBcAg each refer to antibodies to the corresponding antigen.

3. Fulminant hepatitis:
   Much more extensive necrosis of the liver occurs duringthe first 8 weeks of the acute illness.accompanied by high fever; abdominal pain; and eventual renal dysfunction, coma, and seizures.

Clinical significance: chronic disease

In about two thirds of individuals, the primary infection is asymptomatic, though such patients may later develop symptomatic chronic liver disease, indicating persistence of the virus.Adults with immune deficiencies also have high risk of developing chronic infection.

1. Types of chronic carriers:
   asymptomatic carriers of HBsAgare the most common type.
2. Development of hepatocellular carcinoma (hepatoma):
   HBV continuing liver necrosis, followed by regeneration of the damagedtissue, chronic HBV infection provides the opportunity for chromosomal rearrangements and mutations.

Laboratory identification

First, the type of HBV, then either acute or chronic by Elevations of aminotransferases, bilirubin, and prothrombin time all contribute to the initial evaluation of hepatitis.

Treatment

1. Acute hepatitis:
   Not needed, because, in adults, the immune system controls the infection and eliminates the virus within about6 months.
2. Chronic hepatitis:
   Treatment in patients with chronichepatitis is to reduce the risk of progressive chronic liver diseaseand other long-term complications (cirrhosis, carcinoma). commonly useddrugs include interferon-α or one of a large number of nucleoside/nucleotide antiviral agents.

Prevention

1. Active immunization:
   HBsAgis used to prepare vaccines conferring protection because antibody to the virioncomponent neutralizesinfectivity.
2. Passive immunization:
   Immediate administration of HBIG is recommended asthe initial step in preventing infection of individuals accidentallyexposed to HBV-contaminated blood by needlestick or othermeans and of those exposed to infection by sexual contact withan HBV-positive partner.

HEPATITIS D VIRUS (DELTA AGENT)

HDV is found in nature only as a coinfection with HBV.

Structure and replication

(Figure 26.12). HDV RNA genome is replicated and transcribed in the nucleus by cellular enzymes, whose specificity is probably modified by complexing with the delta protein.

Transmission and pathogenesis

Because HDV exists only in association with HBV, it can be transmitted by the same routes.it does not to transmitted sexually as HBV or HIV. HDV usually results in more extensive and severe damage.

Clinical significance

(Figure 26.13)

Laboratory identification

The same methods that used with HBV.

Treatment and prevention

No treatment specific for HDV infection is available.

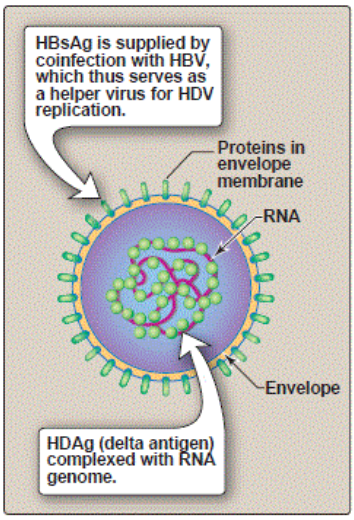
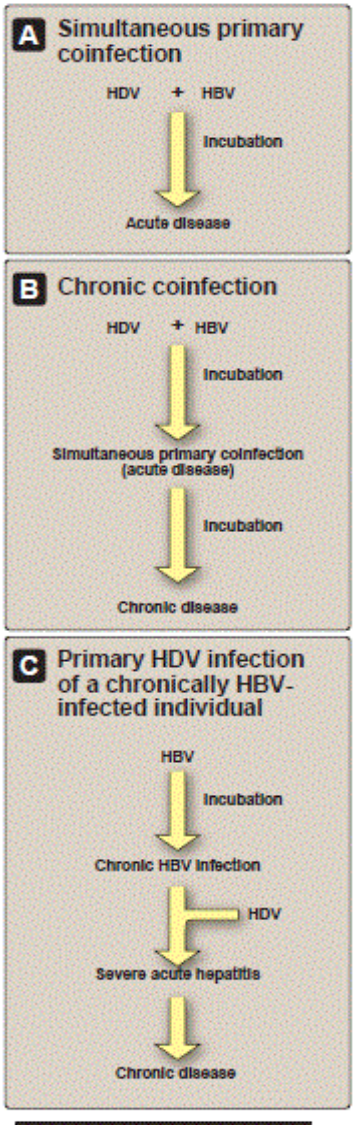


Figure 26.12
Structure of hepatitis D virus.
HBsAg = hepatitis B surface antigen.



CHAPTER 27
Positive-strand; RNA Viruses

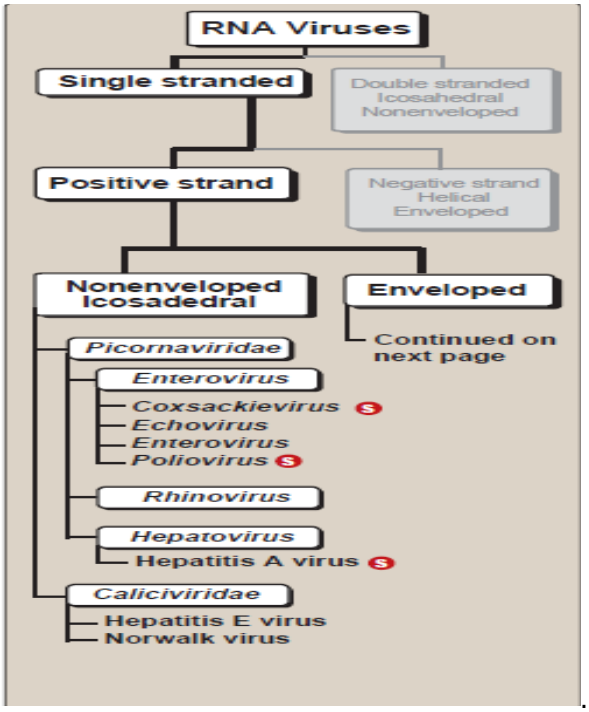
I. OVERVIEW:

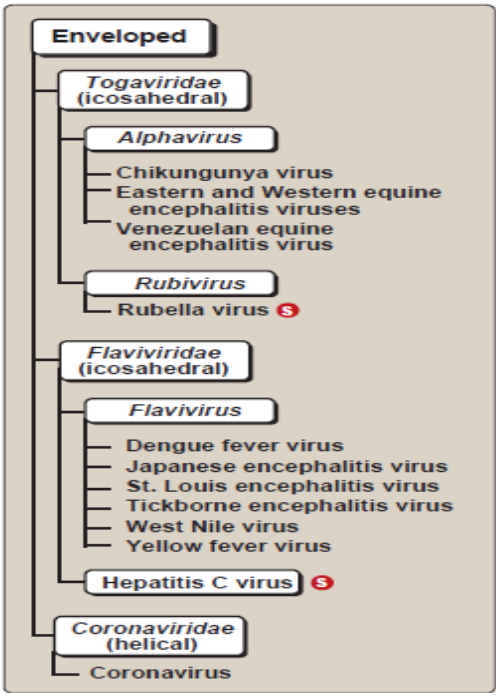
Viruses with a positive-strand RNA genome (that is, one that can serve as a messenger RNA in the infected cell) include the viral families
Picornaviridae, Togaviridae, Flaviviridae, Caliciviridae, and
Coronaviridae.

The viruses in these families cause a broad spectrum of diseases but share the following features:

1) **They replicate in the cytoplasm.**
2) **Genomic RNAs serve as messenger RNAs and are infectious.**
3) **Genomic RNAs are nonsegmented.**
4) **Virions do not contain any enzymes.**
5) **Virus-specified proteins are synthesized as polyproteins.**

That are processed by viral and cellular proteases, giving rise to individual viral
Proteins



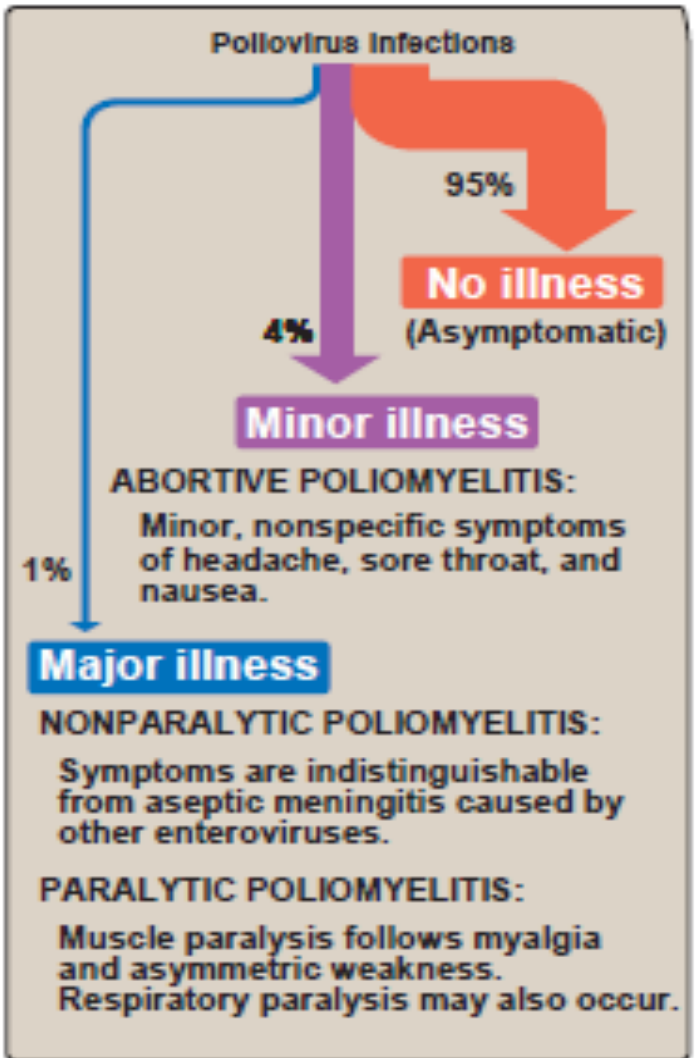


Some positive-strand RNA viruses areenveloped, whereas others are not.

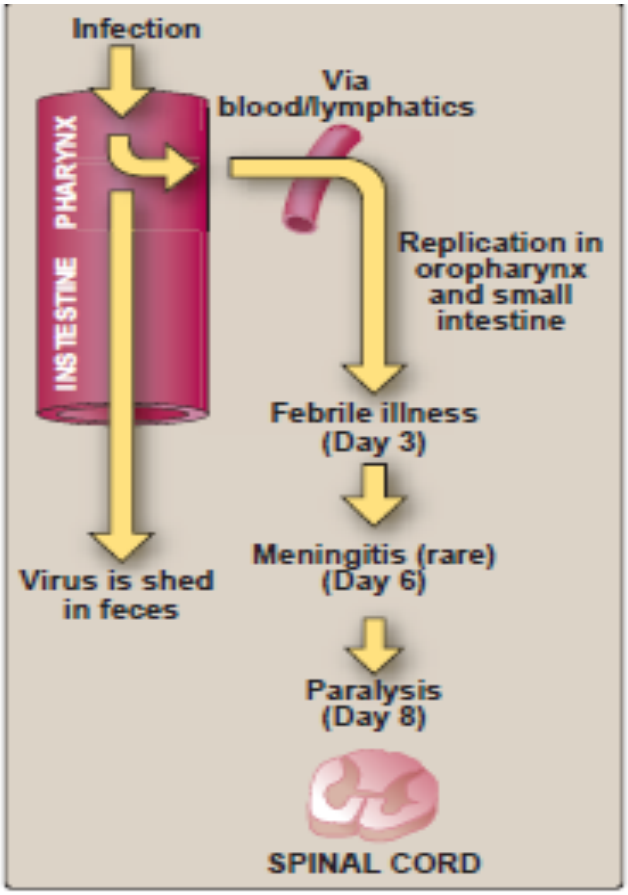
1)PICORNAVIRIDAE:

-Picornaviruses are small, naked (nonenveloped), icosahedral viruses. Which contain a single-stranded, nonsegmented RNA genome and four structural proteins. -Picornaviridae are divided into five genera: enteroviruses ,rhinoviruses, cardioviruses, aphthoviruses, and hepatoviruses.

		Disease		Mode of transmission	Site of replication	Treatment& vacination
Enterovirus Acid stable (Poliovirus)	Coxsackievirus ,Echovirus	1- Asymptomatic infection 95% 2- Abortive infection 4% 3- Paralytic poliomyelitis1%	Meningitis, upper respiratory infections, Gastroenteritis, Herpangina	Fecal–oral route	Binds to a receptor that is a member of the immunoglobulin (Ig)	-Treatment of poliomyelitis are not available. Management is supportive and symptomatic. -Live-attenuated (Sabin) or killed (Salk) polio vaccines.
Rhinovirus Acid labile.		Common-cold syndrome		respiratory droplets, hand-to hand contact.	Replicate efficiently at temperatures several degrees below body temperature (nasal passages)	Because there are more than 100 serotypes of rhinoviruses, development of a vaccine is impractical
Hepatovirus (hepatitis A virus)		viral hepatitis The development of persistent infection and chronic hepatitis is uncommon.		Fecal–oral route. eating uncooked shellfish harvested from sewage-contaminated water.	Hepatocyte	Immune globulin used for many years, mainly as postexposure prophylaxis. vaccination is recommended for children over age 1 year and for persons traveling to developing countries.



Clinical outcomes of infection with poliovirus:



Central nervous system invasion by poliovirus

2) CALICIVIRIDAE:

Caliciviruses are small, nonenveloped, spherical particles. Each contains a single-stranded, nonsegmented RNA genome, and a single species of capsid protein. The Caliciviruses genome contains three open reading frames. Norovirus is theprototype human calicivirus.

	Disease	Mode of transmission	Site pf replication
Caliciviruses Norovirus	Major cause of epidemic acute gastroenteritis, particularly at schools, camps, military bases, prisons, and other closed environments such as cruise ships	Fecal–oral route, following ingestion of contaminated food or water, by person-to-person contact, or by contact with contaminated surfaces	replicates in the GI tract and is shed in the stool.
Hepatitis E virus (HEV)	Major cause of enterically transmitted, waterborne hepatitis A progression to chronic hepatitis is not seen		

3) TOGAVIRIDAE:

The togaviruses are enveloped, icosahedral viruses that contain a positive-sense, single-stranded RNA genome and generally three structural
proteins. The capsid (C) protein encloses the viral RNA, forming the nucleocapsid, and the two other proteins (E1 and E2)

	Disease	Mode of transmission	Site of replication	Laboratory identification	vaccination
Alphavirus which there are approximately 26, are arthropod-borne viruses (arboviruses),	1-Acute encephalitis (Eastern and Western equine encephalitis viruses) 2-Acute arthropathy (Chikungunya virus) 3-A febrile illness with a flulike syndrome (Venezuelan equine encephalitis virus).	Transmitted to humans and domestic animals by mosquitoes Some arboviruses were initially isolated from horses	attachment to the cell surface the virus is internalized by receptor - mediated endocytosis	Rise in antibody titer. Also be isolated from CSF, blood, or tissue. IgM antibody specific for the pathogen can be detected in the CSFof patients suffering from acute infection.	Control of the mosquito vector population. A Venezuelan equine encephalitis vaccine is available.

4) FLAVIVIRIDAE:

Rubivirus	1-Causes a mild clinical syndrome that is characterized by a generalized maculopapular rash and occipital lymphadenopathy. 2-Congenital rubella	Respiratory secretions of an infected person	See the figure below	Antirubella antibodies	Fetal resul from infec preve use atten rubel

The members of this family are enveloped viruses that contain a singlestrandedRNA genome and three structural proteins. The capsid (C)protein and the viral RNA form the icosahedral nucleocapsid, and the other two proteins are envelope associated.

	Disease	Mode of transmission	Site of replication	Laboratory identification	Treatment& vaccination

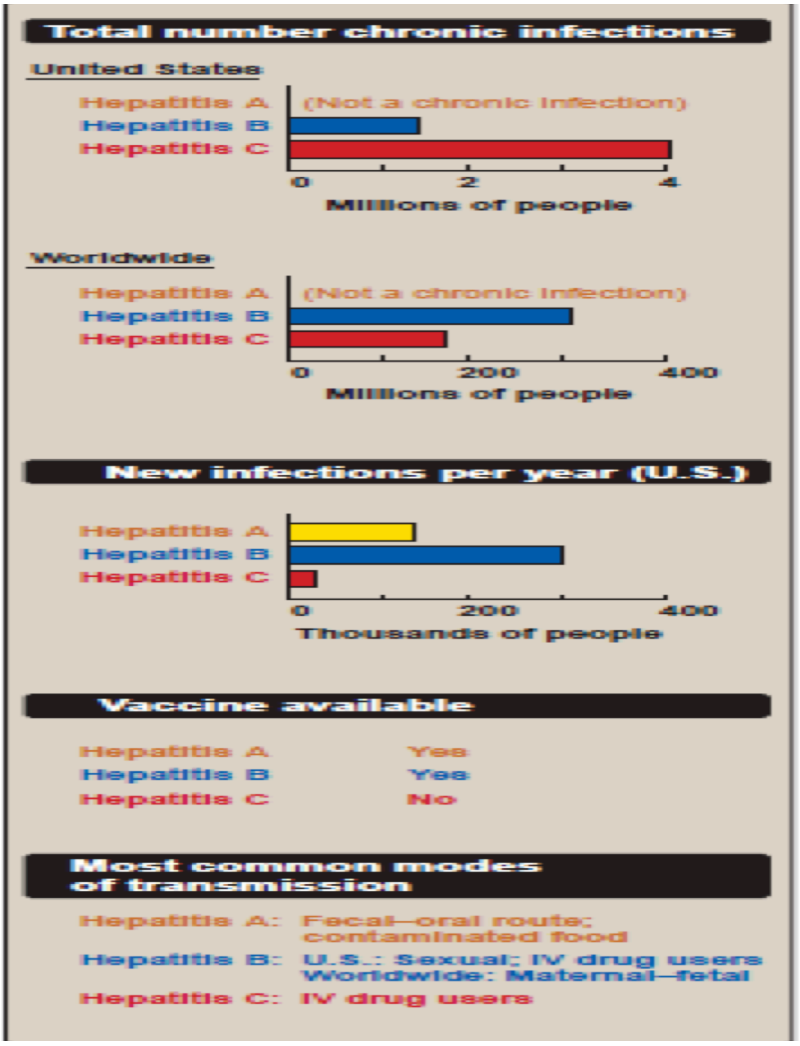
Flavivirus (most of the viruses in this genus are, therefore, arboviruses) yellow fever, St. Louis encephalitis, Japanese encephalitis, dengue fever viruses, and West Nile virus	1-Encephalitis (St. Louis encephalitis 2- Japanese encephalitis 3-Tickborne encephalitis viruses) 4-Hemorrhagic fever (yellow fever virus) 5-Fever, myalgia, and rash (dengue viruses)	Mosquito transmitted. Tickborne encephalitis virus is transmitted by ticks	Maintained in nature by replicating alternately in an arthropod vector and a vertebrate host. Following attachment to the cell surface, the virus is taken up by receptor-mediated endocytosis	At least a fourfold rise in antibody titer. In some cases, virus isolation or demonstration of specific viral antigens is also feasible.	Live attenuated vaccine for yellow Fever. In China and Japan, a formalin-inactivated Japanese encephalitis virus vaccine is used in central Europe, a formalin-inactivated vaccine is widely used to prevent tickborne encephalitis Another important method of prevention is vector control
Hepatitis C viruses	Major cause of posttransfusion hepatitis. infections progress to chronic hepatitis and cirrhosis. Finally, some of these individuals go on to develop hepatocellular carcinoma many years after the primary infection.	-Drug users - patients on hemodialysis are also at high risk. -Tattooing - Sexual transmission -From mother to infant. In the infected individual,	Hepatocyte and, probably, also in mononuclear cells (lymphocytes and macrophages)	Antibodies that react with a combination of recombinant viral proteins. detection of the viral nucleic acid by RT-PCR	Treatment with IFN-© plus ribavirin Chronic hepatitis resulting in severe liver damage may be an indication for a liver transplant.

dengue infection occurs, particularly in infants and young children. Called dengue hemorrhagic fever or dengue shock syndrome, it is associated with a significant mortality (10 percent or higher) if untreated. Like dengue fever, West Nile fever is a mosquito-transmitted,
acute, usually self-limited illness that presents chiefly with
fever, malaise, lymphadenopathy, and rash. Infection may also result in aseptic meningitis or meningoencephalitis, especially in older adults.

5) CORONAVIRIDAE:

Coronaviruses are large, enveloped, pleomorphic particles, with a distinctive arrangement of spikes (peplomers) projecting from their surfaces. [Note: These projections have the appearance of a solar corona, which gives the virus its name.]

The Coronavirus genome is the largest described for any RNA virus thus far. Human coronaviruses have been most commonly implicated in upper respiratory infections, causing 10 percent to 30 percent of cases of the common cold.



CHAPTER 28
Retroviruses and AIDS

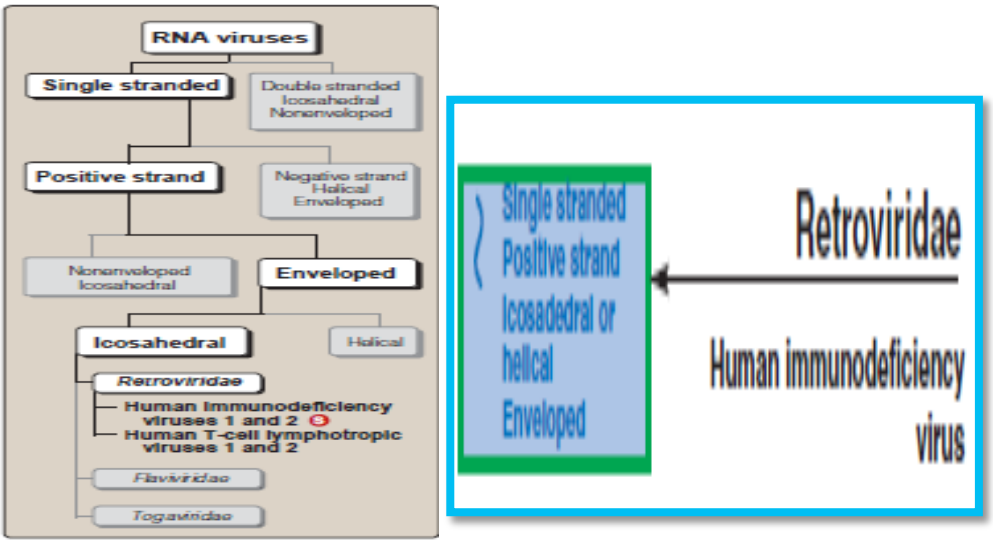
OVERVIEW:

Retroviridae are distinguished from all other RNA viruses by the presence of an unusual enzyme, reverse transcriptase, which converts a single-stranded RNA viral genome into double-stranded viral DNA. Retroviridae contain two genera that are of human interest:

1) Lentivirus, which includeshuman immunodeficiency viruses 1 and 2 (HIV-1 and -2)
2) and 2) the human T-cell lymphotropic virus–bovine leukemia virus group (HTLV-BLV group), which contains human T-cell lymphotropic viruses1and 2(HTLV-1and-2)

RETROVIRUS STRUCTURE:

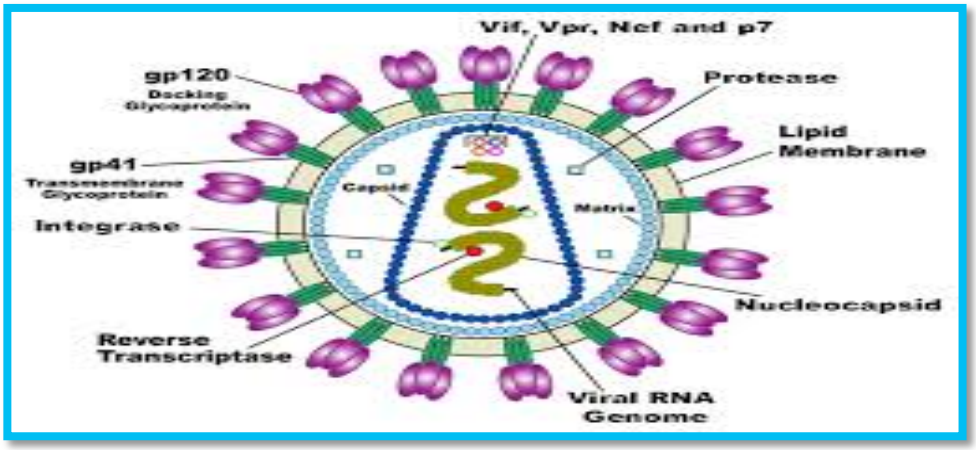
All retroviruses are similar in structure, genome organization, and mode of replication.



Common characteristics:

-Single-stranded, positive-sense, linear RNA; two copies per virion (diploid).
Viral envelope contains glycoprotein that undergoes antigenic variation.
- Virion contains reverse transcriptase.

Structure of the human immunodeficiency virus:



1)HUMAN IMMUNODEFICIENCY VIRUS: (فيروس نقص المناعة)

ما هو الفرق بين فيروس نقص المناعة والإيدز؟

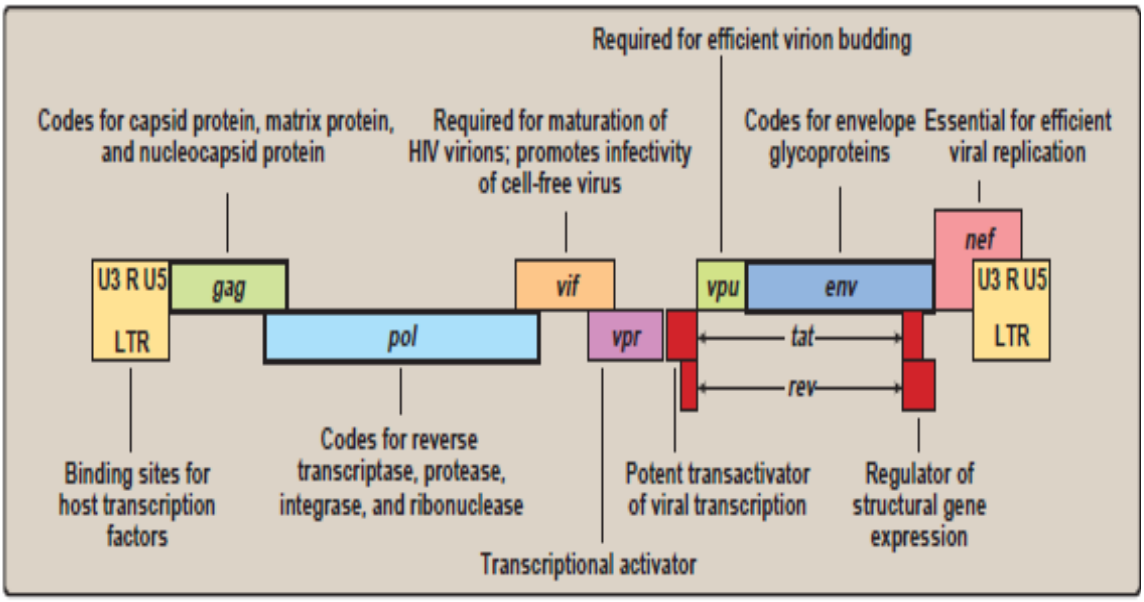
في العادة ما يكتبان بكلمة واحدة تحمل معنى واحداً. ولكن AIDS والإيدزHIVفيروس نقص المناعة هما شيئان مختلفان.AIDS وHIV

HIV) Human Immunodeficiency Virus يصبح) يشير إلى فيروس نقص المناعة في الأنسان.
) عندما يدخل فيروس نقص المناعة إلى مجرى دمه.HIVالشخص مصاباً بفيروس نقص المناعة (إيجابي لـ
فيروس نقص المناعة يهاجم جهاز المناعة في جسم الإنسان، وهو جهاز دفاع الجسم ضد الأمراض. ففي حالة التلف الشديد للجهاز المناعي للشخص عن طريق الفيروس تتطور الأصابة بالفيروس الى مرض الأيدز و الذي يعني متلازمة نقص المناعة المكتسبهAIDS: Acquired Immune Deficiency Syndrome) وهذا يعني أن الجسم)
غير قادر على مكافحة الجراثيم والأمراض العادية ويصبح الشخص أكثر عرضة للإصابة بالأمراض و التي كانت أجسامهم عادةً ما تكافحهم من قبل.

The two types of HIV, HIV-1 and HIV-2, are similar but have different pathogenic potentials and geographic distributions. HIV-1 is more virulent, more infective, and more widespread geographically, whereas HIV-2 is not as virulent.

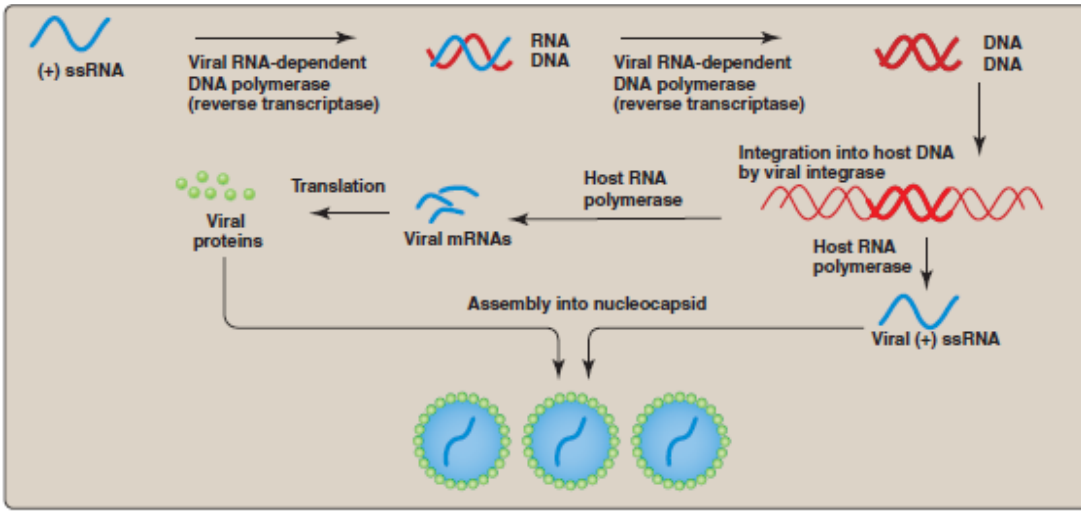
-Organization of the HIV genome:

Human immunodeficiency virus (HIV) proviral genome. The rev and tat genes are divided into noncontiguous pieces, and the gene segments are spliced together in the RNA transcript. LTR = long terminal repeat

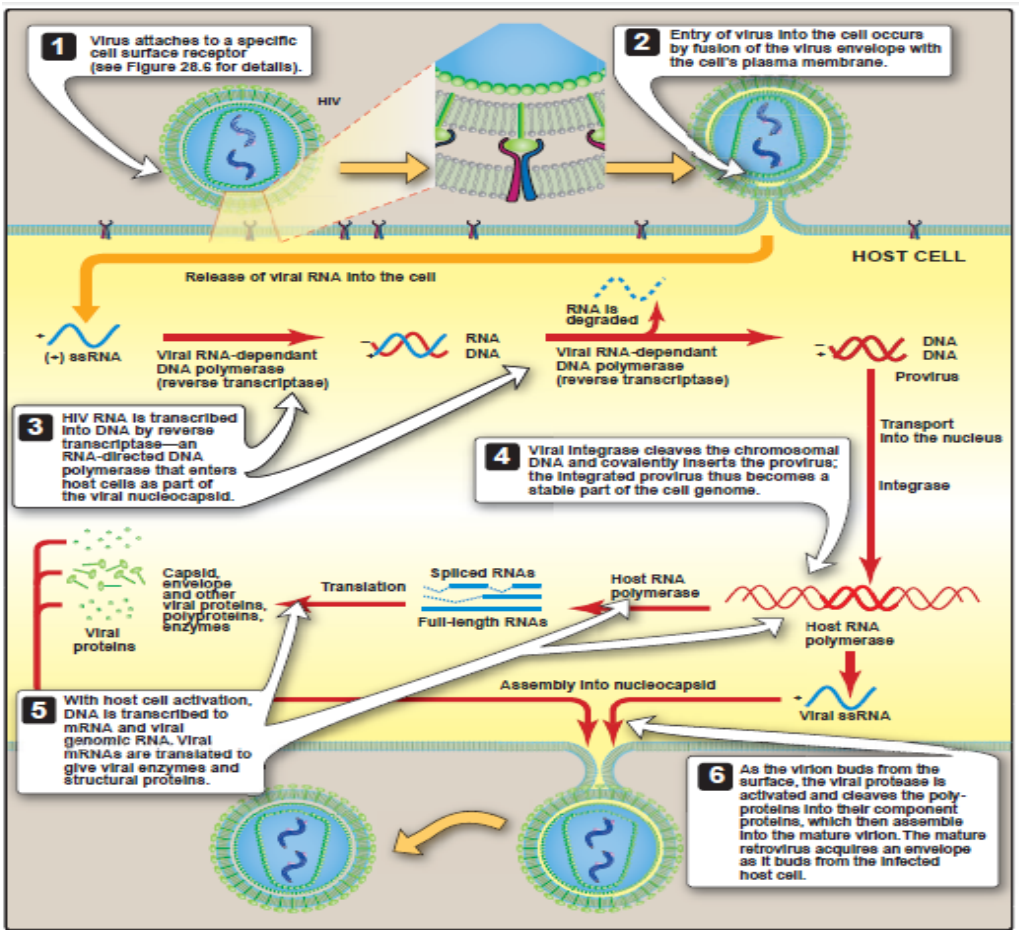


The HIV RNA genome contains three major genes: gag, pol, andenv (Figure 28.5). The gag gene encodes p17 (MA), p24 (CA), andp7 (NC) (core and matrix proteins). The pol gene encodes reverse transcriptase, protease, integrase, and ribonuclease. Finally, the env gene encodes gp41 (TM) and gp120 (SU) (transmembrane and surface proteins). Genes for additional regulatory and accessory proteins of diverse function are located between the pol and env genes.The 5' end of the viral RNA contains a unique sequence, U5, which houses part of the site required for viral integration into the host cell chromosome and also the tRNA primer-binding site for initiation of reverse transcription.The 3' end of the viral RNA contains thenucleotide sequence U3, which houses sequences that are important in the control of transcription of the DNA provirus. As with cellular mRNAs synthesized by RNA polymerase II, the 5' end of the viral RNA synthesized from proviral DNA has a methylated cap, and the 3' end has a poly-A tail. At both ends of the viral genome is a repeated sequence, R, which is involved in reverse transcription. Synthesis of
the double-stranded DNA provirus results in duplication of the R and U sequences, producing two identical repeat units designated long terminal repeats (LTRs).

A brief overview of retrovirus:



HIV replication: The human immunodeficiency virus (HIV) replication cycle. ssRNA = single strand RNA.



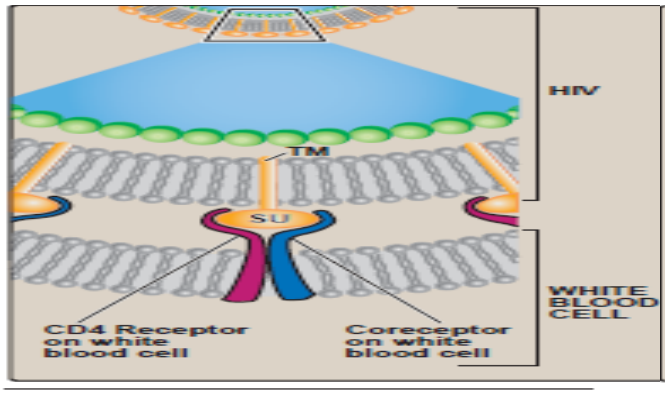


Figure 28.6
Binding of human immunodeficiency virus (HIV) to surface of lymphocyte.

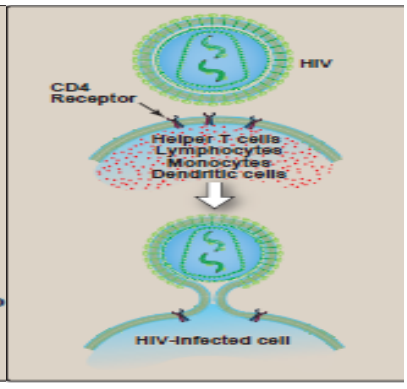
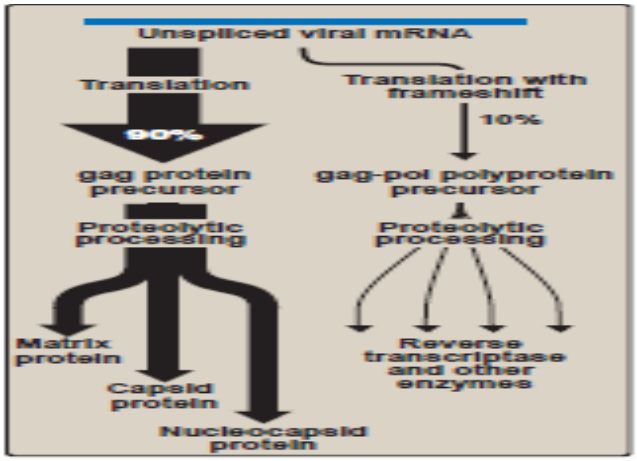


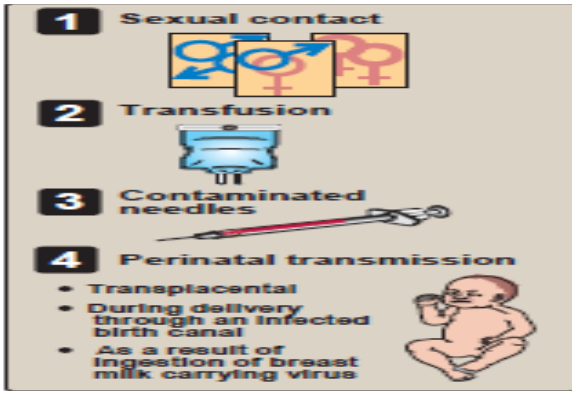
Figure 28.7
Attachment and entry of human immunodeficiency virus (HIV).

Regulation:
Nonstructural genes encode a variety of regulatory proteins that have diverse effects on the host cell and on viral replication. The nef and vpu gene products down-regulate host cell receptors, including CD4 and major histocompatibility complex class I molecules. These products enable efficient virus replication and viron production. The Rev and Tat proteins are produced from differentially spliced mRNAs. The Tat protein causes the host cell RNA polymerase to be more processive by preventing premature dissociation from the DNA template, which results in full-length HIV RNAs. The Rev protein interacts with specific viral mRNAs to enable their transport out of the nucleus,
bypassing the splicing machinery. This process, therefore, enables viral mRNAs to be correctly translated into polypeptides,which will be packaged into new virions.

Assembly and maturation of infectious progeny: Processing of gag and gag-pol polyprotein precursor proteins by the viral protease



Transmission of HIV:



HIV infection:

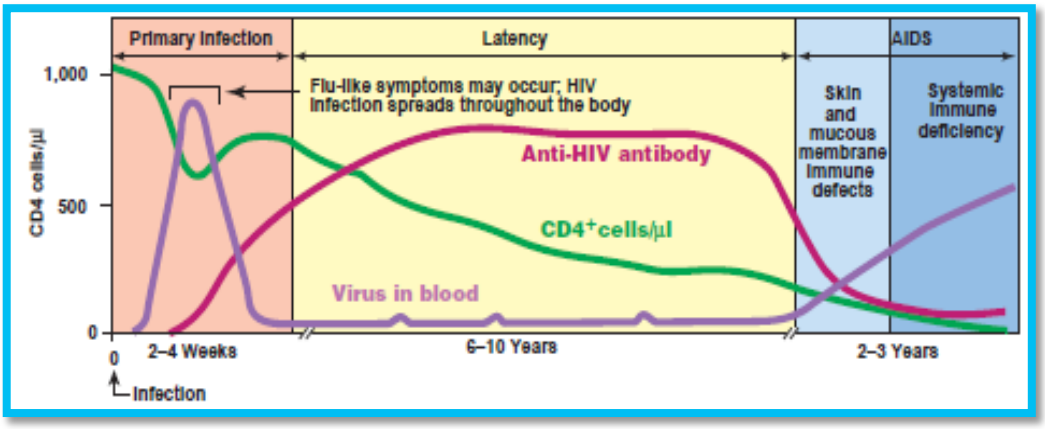
Several weeks after the initial infection, one third to two thirds of individuals experience symptoms similar to those of infectious mononucleosis, during which there is a very high level of virus replication in CD4+ cells. Lymph nodes become infected, which are the sites of virus persistence during the asymptomatic period. The acute phase viremia resolves into a clinically asymptomatic or "latent" period lasting from months to many years. This period is characterized by persistent generalized

lymphadenopathy,diarrhea, and weight loss, opportunistic infections, such as herpes zoster and candidiasis.

Acquired immune deficiency syndrome (AIDS): (الإيدز)

The progression from asymptomatic infection to AIDS occurs as a continuum
of progressive clinical states. The number of infected CD4+ cells decreases, and T-cell precursors in the lymphoid organs are infected and killed, so the capacity to generate new CD4+ cells is gradually lost. Cells of the monocyte/macrophage lineage are also infected, and transport the virus into other organs, including the brain. When the CD4+ count falls below 200/ìl, and increasingly frequent and serious opportunistic infections appear, the syndrome is defined as AID

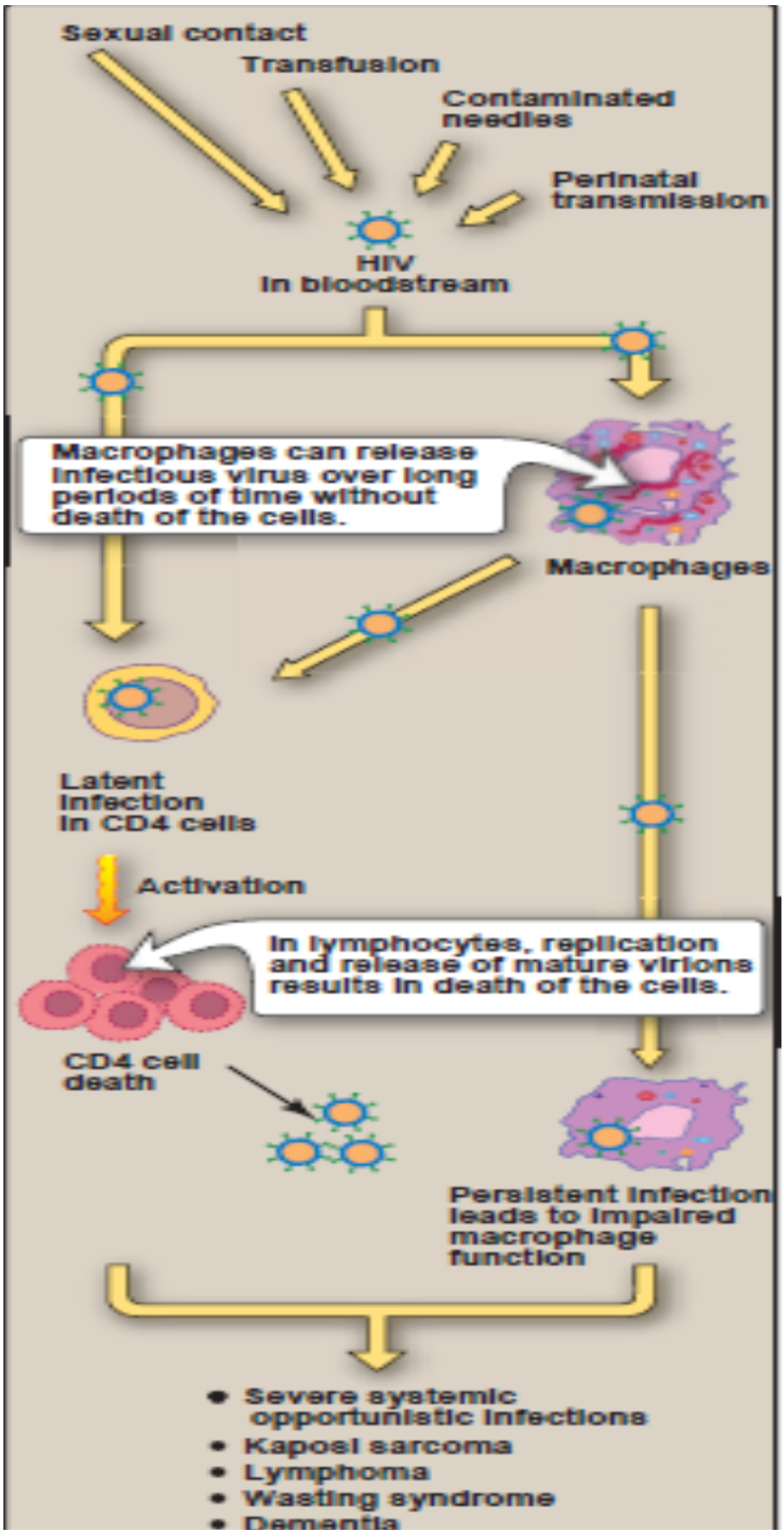
Typical time course of human immunodeficiency virus (HIV) infection.



End-stage AIDS:

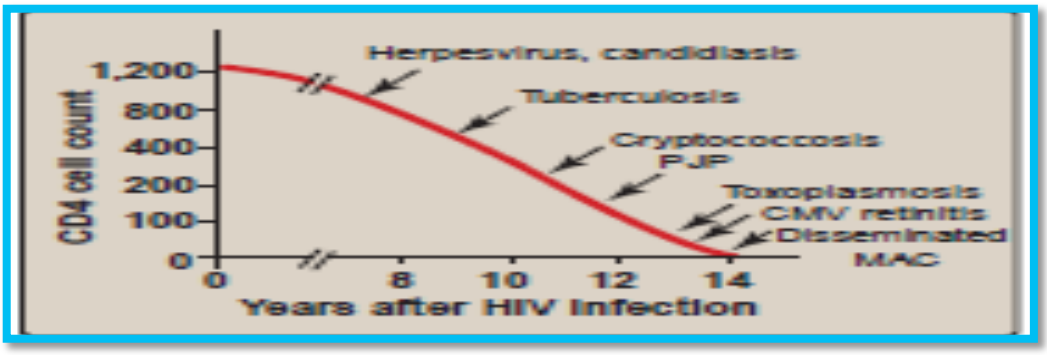
Nearly all systems of the body can be affected as a result of HIV infection, either by HIV itself or by opportunistic organisms. The weakening immune system leads to many complications, including malignancies

Spread of HIV to additional body sites:



Opportunistic infections in AIDS:

Pattern of opportunistic infections associated with declining CD4+ cell counts. CMV = cytomegalovirus;MAC = *Mycobacterium avium* complex;PJP = *Pneumocystis jiroveci* pneumonia; HIV = human immunodeficiency virus.



Malignancies associated with AIDS:

A number of malignancies commonly arise in HIV-infected patients. The most characteristic neoplasm present in AIDS patients is Kaposi sarcoma, which involves skin, mucous membranes, and deep viscera. Various lymphomas, including those of the central nervous system (CNS), are also common. These are probably the result of the immune compromise and not HIV itself.

Laboratory identification:

-Amplification of viral RNA or DNA proviruses by the polymerase chain reaction technique is the most sensitive method for detection of virus in blood or tissue specimens.

- For purposes of screening the blood supply, enzymelinked immunosorbent assay (ELISA) testing for the p24 (CA) antigen in serum can detect infection about a week earlier than tests for antibody.

- For screening individuals, the ELISA procedure is also used to detect antibodies in serum. Any positive results must be confirmed using the Western blot technique.

Treatment:

Inhibitors of viral reverse transcriptase include both nucleoside and non-nucleoside reverse transcriptase inhibitors. They prevent the establishment of HIV infection. Inhibitors of the viral protease delay the production of progeny virus. Because administering combinations of these drugs delays the appearance of resistant mutants, 3 or 4 drugs are given at the same time. This is referred to as "highly active anti-retroviral therapy" or HAART.

Highly active antiretroviral therapy (HAART). 1Choice of a drug regimen is individualized based on criteria such as tolerability, drug–drug interactions, convenience/adherence, and possible baseline resistance. The availability of well-tolerated combination antiretroviral tablets that can be dosed once daily has greatly simplified early treatment of human immunodeficiency virus infection. CCR5 = C-C chemokine receptor type 5 that can function as viral coreceptor.

Perinatal treatment:

Zidovudine when administered to HIV-1–infected pregnant women during the second and third trimesters of pregnancy, followed by administration to the infants during the first 6 weeks of life, reduces risk of maternal–infant transmission of HIV-1 from approximately 23 percent to 8 percent.

Pre-exposure prophylaxis: Truvada, a once-daily tablet containing tenofovir and emtricitabine, significantly reduced the risk of acquiring HIV infection. The drug is already approved to treat HIV infection but must be used in combination with other drugs to prevent the emergence of resistant HIV strains. The drug is useful for people at high risk of infection, like MSM with multiple sex partners, and individuals who are in relationships with someone who is HIV positive.

Prevention:

No vaccine is available. Perinatal transmission can be reduced with zidovudine (AZT) therapy of the pregnant woman, followed by several weeks of AZT tothe newborn. Prevention can be achieved by screening blood and tissues prior to transfusion or transplant, using condoms during sexual intercourse, and strict adherence to universal precautions by health care workers.

2) HUMAN T-CELL LYMPHOTROPIC VIRUSES,TYPES 1 AND 2:

Human T-cell lymphotropic viruses, types 1 and 2 (HTLV-1 and -2) are genetically and biologically similar. However, their worldwide distributiondiffers. HTLV-1 has definitively been associated with a human malignant disease, adult T-cell leukemia (ATL), and a less common neurologic condition, HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP). There are six subclasses of HTLV-1, each of which is endemic to different regions of the world. No conclusive evidence links HTLV-2 to any known disease.

Transmission of HTLV:

HTLV transmission occurs primarily by cell-associated virus, via one of three routes.

1- in highlyendemic regions, mother to fetus or newborn is the most common mode of transmission. This is accomplished via infected lymphocytes either transplacentally or in breast milk.

2- infection can be transmitted sexually by infected lymphocytes contained in semen.

3- any blood products containing intact cells are also a potential source of infection. There is little evidence for transmission by cell-free fluids.

Pathogenesis and clinical significance of adult T-cell leukemia:

Both HTLV-1 and HTLV-2 infect lymphocytes: HTLV-1 has a tropism for CD4 lymphocytes, whereas HTLV-2 preferentially infects CD8 lymphocytes. HTLV-1 infection both stimulates mitosis and immortalizes T lymphocytes, which acquire an “antigen-activated” phenotype.

Following infection, the virus becomes integrated in the host cell as a provirus and transforms a polyclonal population of T cells. Continued multiplication of T lymphocytes over a period of many years results in the accumulation of many chromosomal aberrations. Peripheral blood smears show lymphoid cells with hyper lobulated nuclei.

HTLV-I seroprevalence ratesare strongly age- and sex-dependent, with higher rates associatedwith older age and with female sex The majority of infected individuals are asymptomatic carriers who have an estimated 2 to 4 percent chance of developing ATL within their lifetime. ATL typically appears 20 to 30 years after initial infection, when an increasingly larger population of monoclonal malignant ATL cells develops. Median survival after appearance of acute ATL is about 6 months.

Pathogenesis and clinical significance of HTLV-associated myelopathy/tropical spastic paraparesis:

About 1 to 2 percent of HTLV-1–infected individuals will go on to develop HAM/TSP. HAM/TSP is distinctly different from ATL in that it usually appears only a few years after infection. CNS involvement is indicated by:

1) the presence of anti-HTLV-1 antibody in the cerebrospinal fluid,
2) lymphocytic infiltration and demyelination of the thoracic spinal cord,
3) brain lesions. The lymphocyte count is normal, although there is a polyclonal nonmalignant fraction with integrated HTLV. HAM occurs with lower frequency than ATL among HTLV-infected populations. It is characterized by progressive spasticity and weakness of the extremities, urinary and fecal incontinence, hyperreflexia, and some peripheral sensory loss.

Other manifestions of HTLV-1 infection.

HTLV-1 infections have also been associated with uveitis and retinal vasculitis. In addition, a chronic, severe form of infectious dermatitis can result from vertical transmission of the HTLV-1 virus and has been linked with an earlier onset of HAM/TSP.

Laboratory identification

Screening of blood donors for HTLV is done by ELISA or agglutination tests but the existence of false-positives necessitates confirmatory testing by Western blotting. Test sensitivity is also a problem caused by the low and variable antibody titers in infected individuals. PCR amplification can be used to distinguish between HTLV-1 and HTLV-2 infections and to quantify viral load, which is a marker for the progression to HAM/TSP.

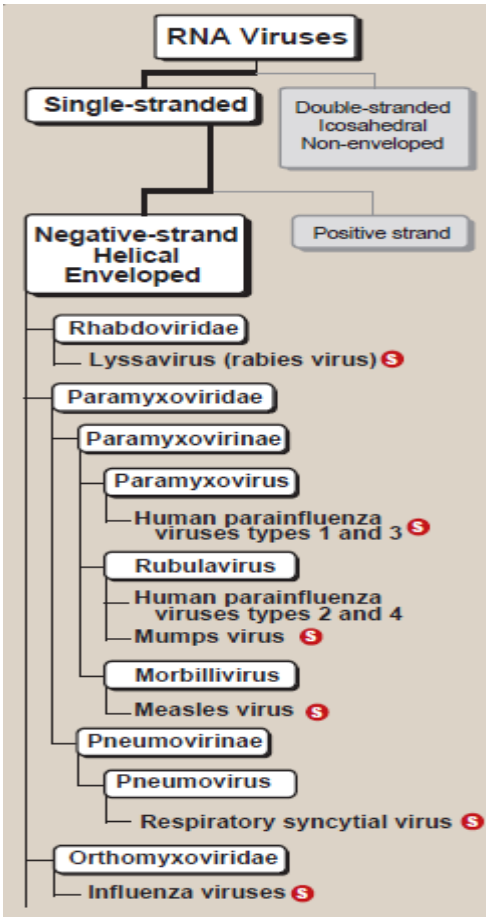
Treatment and prevention

The usual agents used in cancer chemotherapy have proven to be ineffective in treating ATL, and attempts to treat HAM/TSP, for the most part, have been equally unsuccessful. Treatment of both diseases is symptomatic. An estimated 15 to 20 million people worldwide are infected with HTLV-1 or -2, and 5 percent of these will eventually develop either ATL or HAM/TSP.

CHAPTER 29
NEGATIVE-STRAND RNA VIRUSES

OVERVIEW:

Medically important negative-strand RNA viruses are shown in Figure. They have several things in common: 1) they are all enveloped; 2) their virions contain an RNA-dependent RNA transcriptase that synthesizes viral mRNAs using the genomic negative-strand RNA as a template; 3) the genomic negative-strand viral RNAs are not infectious, in contrast to the genomic RNAs of positive-strand viruses; and 4) following entry and penetration, the first step in the replication of negative-strand RNA viruses is the synthesis of mRNAs, whereas with positive-strand RNA viruses, the first step in replication is translation of the incoming genomic RNA (see p. 239). Some negative-strand RNA viruses have segmented genomes, whereas others have nonsegmented genomes. Although most of these viruses replicate in the cytosol, the replication of influenza virus RNA (an orthomyxovirus) occurs in the nucleus.



FAMILY RHABDOVIRIDAE:

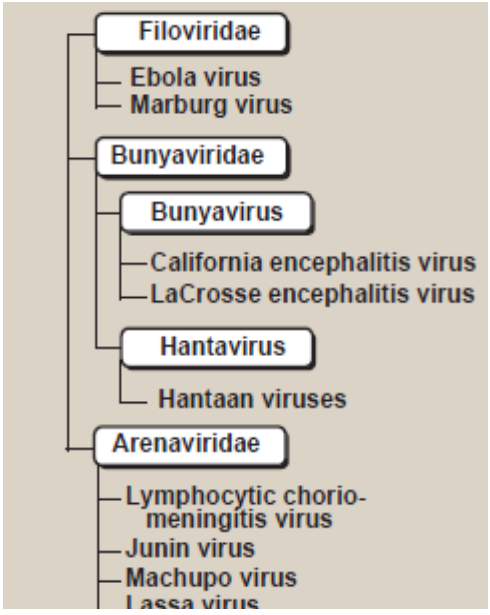
Rhabdoviruses are enveloped, bullet-shaped viruses. Each contains a helical nucleocapsid. The viruses in the family Rhabdoviridae known to infect mammals are divided into two genera: Lyssavirus (rabies virus, the rhabdovirus of greatest medical importance to humans), and Vesiculovirus [vesicular stomatitis virus (VSV), a virus of horses and cattle, and the best studied virus in this family]. Other rhabdoviruses infect invertebrates, plants, or other vertebrates.

A. Epidemiology:

A wide variety of wildlife, such as raccoons, skunks, squirrels, foxes, and bats, provide a reservoir for the rabies virus. In third-world countries, domestic dogs and cats also constitute an important reservoir for rabies. Humans are usually infected by the bite of an animal, but in some cases, infection is via an aerosol (for example, of droppings from infected bats).

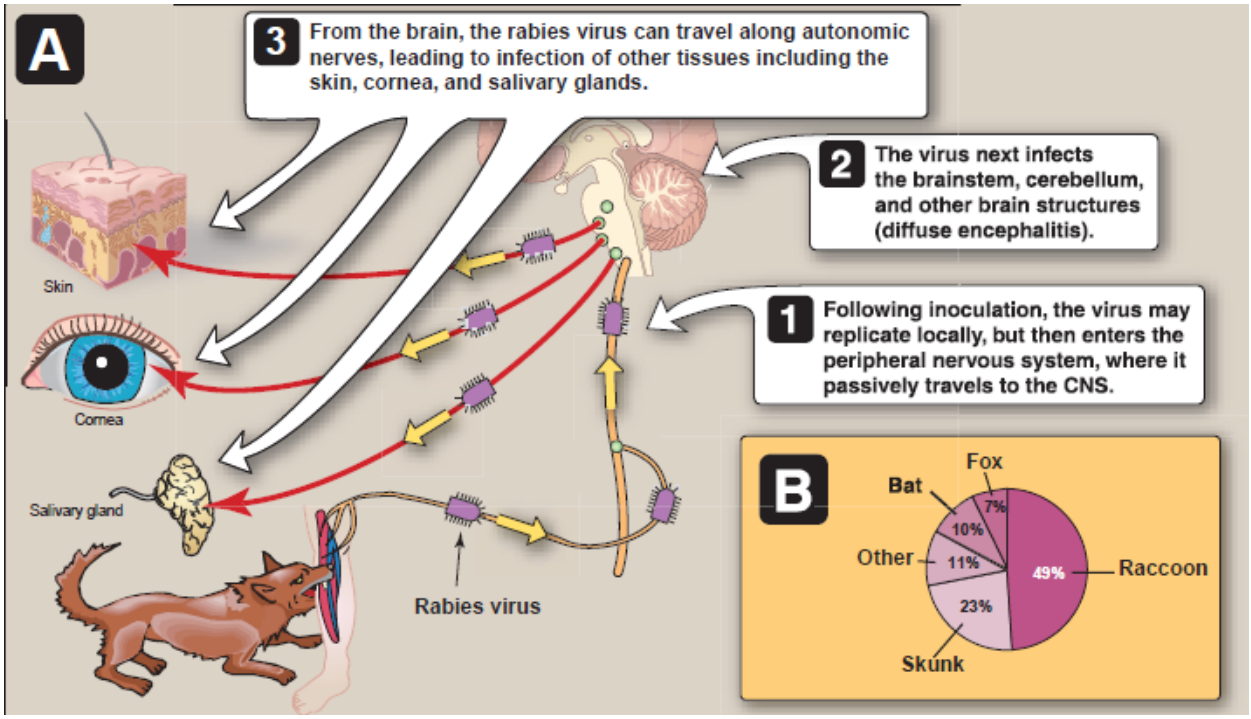
B. Viral replication:

The genomic negative-strand RNA is nonsegmented. The virion contains five proteins, one of which, the G (for glyco-) protein, is an envelope protein that comprises viral spikes. The rabies virion attaches via its glycoprotein spikes to cell-surface receptors. Entry into the cell is by receptor-mediated endocytosis, following which the viral envelope fuses with the endocytotic vesicle's membrane, releasing the viral



nucleocapsid into the cytosol where replication occurs. Five different mRNAs are transcribed from the genomic RNA template by the virion's RNA-dependent RNA polymerase (transcriptase function), and each encodes one of five viral proteins. This process is an example of the Type II virus genome replication described on p. 240. Viral structural proteins plus the negative-strand viral RNA form new helical nucleocapsids, which move to the cell surface. There, each nucleocapsid acquires its envelope by budding through a region of virus-modified plasma membrane.

C. Pathology:



D. Laboratory identification:

Clinically, diagnosis rests on a history of exposure and signs and symptoms characteristic of rabies. However, a reliable history of exposure is often not obtainable, and the clinical presentation, especially in the initial stages, may not be characteristic. Therefore, a clinical diagnosis may be difficult. Postmortem, in approximately eighty percent of cases, characteristic eosinophilic cytoplasmic inclusions (Negri bodies) may be identified in certain regions of the brain, such as the hippocampus; these inclusion bodies are diagnostic of rabies. Prior to death, the diagnosis can be made by identification of viral antigens in biopsies of skin from the back of the neck or from corneal cells or by demonstration of the viral nucleic acid by RT-PCR.

E. Treatment and prevention:

Once an individual has clinical symptoms of rabies, there is no effective treatment. However, a killed rabies virus vaccine is available for prophylaxis. In the United States, this is generally the human diploid cell vaccine (HDCV). Preexposure prophylaxis is indicated for individuals at high risk because of the work they do (for example, for veterinarians). Postexposure prophylaxis refers to treatment instituted after an animal bite or exposure to an animal (or human) suspected of being rabid, and consists of thorough cleaning of the wound, passive

immunization with antirabies immunoglobulin, and active immunization with the rabies vaccine (HDCV). Prevention of initial exposure is, however, clearly the most important mechanism for controlling human rabies.

FAMILY PARAMYXOVIRIDAE:

The members of the paramyxovirus family have recently been subdivided into two subfamilies. First, the Paramyxovirinae, whose three genera include: 1) Paramyxovirus (parainfluenza viruses, which cause upper respiratory tract infections); 2) the Rubulavirus (mumps virus); and 3) the morbillivirus (measles virus). The second subfamily is the Pneumovirinae, which includes respiratory syncytial virus, a major respiratory tract pathogen in the pediatric population. Paramyxoviruses are spherical, enveloped particles that contain a nonsegmented, negative- strand RNA genome. Paramyxoviridae typically consist of a helical nucleocapsid, surrounded by an envelope that contains two types of integral membrane or envelope proteins. The first, the HN protein, is involved in the binding of the virus to a cell; measles virus lacks the neuraminidase activity. The second, the F protein, functions to fuse viral and cellular membranes, thus facilitating virus entry into the cytoplasm where viral replication occurs. Paramyxovirus mRNA transcription, genome replication, and viral assembly and release, resemble those of the rhabdoviruses.

A. Genus Paramyxovirus:

The clinically important viruses in this genus are type 1 and type 3 human parainfluenza viruses (hPIV). They cause croup, pneumonia and bronchiolitis, mainly in infants and children. The term “parainfluenza” was first coined because infected individuals may present with influenza-like symptoms, and, like influenza virus, these viruses have both hemagglutinating and neuraminidase activities.

B. Genus Rubulavirus:

This genus contains hPIV type 2 and type 4 and mumps virus.

1. Type 2 and type 4 human parainfluenza viruses: The clinical features of infection with parainfluenza virus type 2 are similar to those of types 1 and 3 viruses. Type 4 hPIV has been associated only with a mild upper respiratory tract illness, affecting both children and adults.

2. Mumps virus: Mumps used to be one of the commonly acquired childhood infections. Adults who escape the disease in childhood could also be infected. In the prevaccine period, mumps was the most common cause of viral encephalitis. Complete recovery, however, was almost always the rule. The virus is spread by respiratory droplets. Although about one third of infections are subclinical, the classic clinical presentation and diagnosis center on infection and swelling of the salivary glands, primarily the parotid glands. However, infection is widespread in the body and may involve not only the salivary glands but also the pancreas, CNS, and testes. Orchitis caused by mumps virus may cause sterility. A live, attenuated vaccine has been available for many years; this has resulted in a dramatic drop in the number of cases of mumps.

C. Genus Morbillivirus:

Measles virus (MV) is the only virus in this genus that causes disease in humans. Other viruses in the genus morbillivirus are responsible for diseases in animals (canine distemper virus). Measles virus differs in several ways from the other viruses in the family Paramyxoviridae.

1. Viral replication: The cellular receptor for measles virus is the CD46 molecule, a protein whose normal function is to bind certain components of complement. Although the viral attachment protein has hemagglutinating activity, it lacks neuraminidase activity. Hence, it is referred to as the H protein, rather than HN protein. A fusion (F) protein facilitates uptake of the virion. Measles virus replication in tissue culture and certain organs of the intact organism is characterized by the formation of giant multinucleate cells (syncytium formation), resulting from the action of the viral spike F protein.

2. Pathology: Measles virus is transmitted by sneeze- or coughproduced respiratory droplets. The virus is extremely infectious, and almost all infected individuals develop a clinical illness. Measles virus replicates initially in the respiratory epithelium and then in various lymphoid organs. Classically, measles begins with a prodromal period of fever, upper respiratory tract symptoms, and conjunctivitis. Two to three days later, specific diagnostic signs develop; first, Koplik spots and then a generalized macular rash, beginning at the head and traveling slowly to the lower extremities. Soon after the rash appears, the patient is no longer infectious. The major morbidity and mortality caused by measles are associated with various complications of infection, especially those affecting the lower respiratory tract and the CNS. The most important of these is postinfectious encephalomyelitis, which is estimated to affect 1 of 1,000 cases of measles, usually occurring within two weeks after the onset of the rash. This is an autoimmune disease associated with an immune response to myelin basic protein. Figure 29.9 shows the time course of measles virus infection.

3. Diagnosis: In most cases, there is little difficulty in making a diagnosis of measles on clinical grounds, especially in an epidemic situation. The presence of Koplik spots provides a definitive diagnosis. If a laboratory diagnosis is necessary, it is usually made by demonstrating an increase in the titer of antiviral antibodies.

4. Prevention: Measles is usually a disease of childhood, and is followed by life-long immunity. A live, attenuated measles vaccine, which has been available for many years, has greatly reduced the incidence of the disease. Nevertheless, occasional outbreaks of measles continue to occur, especially in older children and young adults, possibly due to waning immunity. Thus, two doses of the vaccine, in the form of the measles-mumps-rubella (MMR) vaccine, are now recommended, the first at twelve to eighteen months, the second at four to twelve years.

D. Genus pneumovirus:

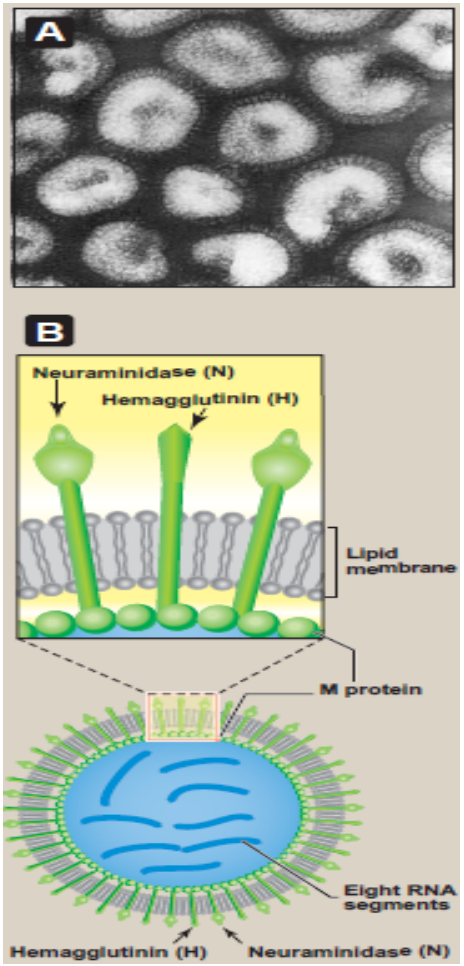
The one virus in this genus that is of medical importance is respiratory syncytial virus (RSV). RSV is the major viral respiratory tract pathogen in the pediatric population, and the most important cause of bronchiolitis in infants. RSV may also cause pneumonia in young children, an influenza-like syndrome in adults, and severe bronchitis with pneumonia in the elderly and organ transplant recipients. The viruses in the subfamily Pneumovirinae, genus Pneumovirus, are set apart from those in the other three genera in the Paromyxovirus family by a somewhat more complex genome and a larger number of virus-specific proteins. Nevertheless, the basic strategy of replication is as described for the other viruses in this family. RSV has one envelope protein that functions as an attachment protein and another that functions as a fusion protein; however, like measles virus, RSV lacks neuraminidase activity. RSV is transmitted by respiratory droplets or by contaminated hands carrying the virus to the nose or mouth. Repeated infections are common. A definitive diagnosis of RSV infection can be made only on the basis of laboratory findings, such as a rise in the titer of serum antibody or the demonstration of viral antigens in respiratory secretions. The only

specific treatment is ribavirin, administered by aerosol, and this is only of moderate benefit. Hand-washing and avoidance of others with the infection are the major preventive measures.

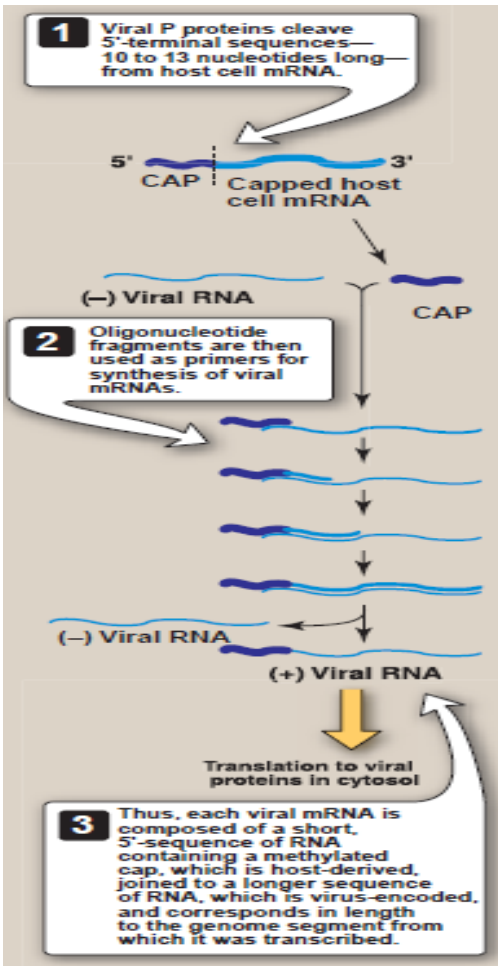
FAMILY ORTHOMYXOVIRIDAE:

Orthomyxoviruses are spherical, enveloped viruses containing a segmented, negative-strand RNA genome. Viruses in this family infect humans, horses, and pigs, as well as nondomestic water fowl, and are the cause of influenza. Orthomyxoviruses are divided into 3 types: influenza A, B, and C. Only influenza virus types A and B are of medical importance. Type A influenza viruses differ from type B viruses in that they have an animal reservoir and are divided into subtypes.

A. Structure:



B. Viral replication:



C. Pathology and clinical significance:

In humans, influenza is spread by respiratory droplets and is an infection solely of the respiratory tract. There is rarely viremia or spread to other organ systems. Destruction of respiratory epithelial cells is attributed to the host immune response, specifically cytotoxic T cells. Typically, influenza has an acute onset characterized by chills, followed by high fever,

muscle aches, and extreme drowsiness. The disease runs its course in four to five days, after which there is a gradual recovery. The most serious problems, such as development of pneumonia, occur in the very young, the elderly, and people with chronic cardiac or pulmonary disease or those who are immunodeficient.

. The immunology of influenza viruses:

When individuals are infected with influenza virus, antibodies are made against the various viral proteins. However, it is the antibodies made against the H protein that are neutralizing and the best index of protection. The antigenic properties of the influenza virus proteins are also important because they serve as the basis for the classification of influenza viruses.

E. Diagnosis:

The collection of influenza-like symptoms described above can also be caused by other viruses. Therefore, a definitive diagnosis cannot be made on clinical grounds except in an epidemic situation. In most cases, it is not practical to make a specific laboratory diagnosis. However, if needed for surveillance purposes, for example, a widely performed and specific test is the quantitation of HI (hemagglutination inhibition) antibodies. This has the added advantage of identifying the subtype of the virus. A more rapid diagnosis can be made by the demonstration of viral antigens in respiratory tract secretions.

F. Treatment and prevention:

1. Amantadine and rimantadine: First-generation antiviral agents effective against influenza A include two related drugs, amantadine and rimantadine. Both drugs stop viral uncoating by inhibition of the viral M2 membrane protein. These agents reduce both the duration and the severity of flu symptoms, but only if given early in infection. Given before the onset of symptoms, these drugs can also prevent disease. The usefulness of amantadine and rimantidine has been limited by a combination of problems: 1) lack of efficacy against influenza B virus, 2) rapid emergence of drug-resistant variants of the virus, and 3) neurologic adverse effects. Currently, amantadine and rimantadine are not recommended for treatment or prophylaxis of influenza in the United States until susceptibility to the drugs has been reestablished among circulating influenza A isolates.

2. Zanamivir and oseltamivir: Second-generation antiviral agents effective against influenza A and B include zanamivir and oseltamivir. They inhibit viral neuraminidase, which is present in both influenza A and B viruses. The drugs are indicated for uncomplicated acute illness in adults and adolescents twelve years of age and older who have been symptomatic for no more than two days. Zanamivir must be taken by inhalation. In contrast, oseltamivir is well absorbed when administered orally, and has proven to be effective for symptomatic patients as well as for prophylaxis. For maximum benefit, therapy should begin within two days of symptom onset. For example, oseltamivir taken within 24 hours of symptom onset shortened the duration of illness by about two days, with patients reporting feeling better within a day of starting treatment.

3. Vaccine: As useful as new therapies are, they are not a substitute for the vaccine. A vaccine consisting of formalin-inactivated influenza virus has been available for many years. It is recommended for the elderly and for people in high-risk groups, such as patients with

chronic pulmonary or cardiac disease. It is of critical importance that the vaccine contain the specific subtypes of influenza virus that are in circulation at any given time.

FAMILY FILOVIRIDAE:

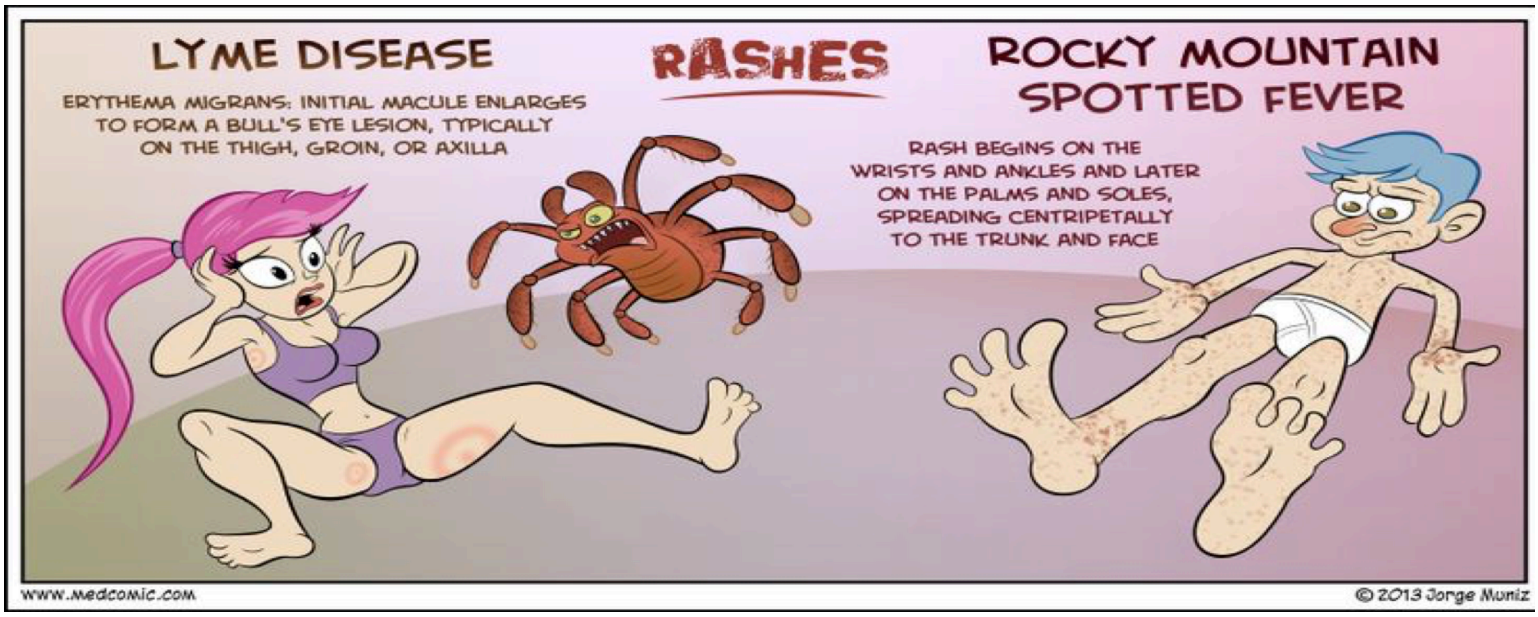
Filoviruses are pleomorphic viruses with unusual morphologies. They are generally seen as long, filamentous, enveloped particles that may be branched. Marburg virus was initially isolated in Germany and Yugoslavia from laboratory workers who became severely ill while preparing primary cell cultures from African green monkeys. Ebola virus was isolated from patients with hemorrhagic fever in Zaire and the Sudan. The two viruses are not related antigenically. Marburg and Ebola viruses cause severe hemorrhagic fever, characterized by widespread bleeding into the skin, mucous membranes, visceral organs, and the gastrointestinal tract. The mortality rate is high, often greater than fifty percent. Although the natural reservoir for these viruses is unknown, they can be transmitted to humans from infected monkeys and probably other animals or by exposure to blood or other body fluids from an infected patient. Outbreaks of hemorrhagic fever caused by these viruses continue to occur at irregular intervals. Laboratory identification is made by the demonstration of antiviral antibodies, for example, by ELISA assays. If virus can be recovered, the morphology of the particles is quite characteristic. There is no specific treatment for infections caused by these viruses. Strict barrier nursing techniques are essential when caring for infected individuals. Because of the hazards of working with filoviruses, they are studied in only a few reference laboratories around the world.

FAMILY BUNYAVIRIDAE:

In the United States, the clinically most important viruses in this family are California encephalitis and LaCrosse viruses (genus, Bunyavirus), which cause meningitis and encephalitis, and the Hantaan viruses (genus, Hantavirus), which are associated with hemorrhagic fever with or without renal syndrome, and hantavirus pulmonary syndrome, a condition associated with high mortality. The viruses in this family are spherical, enveloped particles, with spikes projecting from the surface of the virions. Because the RNA genome is divided into three segments, reassortment of RNA segments between closely related viruses is possible. Arthropods serve as vectors for most viruses in the family Bunyaviridae that are transmitted to humans. However, because viruses in the genus Hantavirus do not have an arthropod vector, they are transmitted to humans by rodents via aerosols formed from their dried excretions. No effective antiviral agent is currently available.

FAMILY ARENAVIRIDAE:

Arenaviruses are enveloped, spherical particles with a bipartite (twosegment) RNA genome that exists in virions as helical nucleocapsids. Both RNAs have an ambisense organization, which means that coding information is contained in both the genomic and antigenomic viral RNAs. Viral particles mature by budding from the plasma membrane. Viruses in this family are associated with chronic infections of rodents, and humans are infected by inhaling contaminated aerosols, eating food containing viral particles, or by exposure of open wounds to infected soil. Lymphocytic choriomeningitis (LCM) virus, a cause of viral meningitis, is a relatively benign infection with little mortality. In Latin America, Junin and Machupo viruses are associated with Argentine and Bolivian hemorrhagic fevers, respectively; these are diseases with mortality rates of 25 to thirty percent. In Africa, Lassa fever (caused by Lassa virus) is a severe infection that is associated with bleeding and an expected mortality rate of about fifteen percent. Ribavirin appears to be of benefit both in Lassa fever and hemorrhagic fevers. The most important measure in prevention, however, is rodent control.


LYME DISEASE
RASHES
ROCKY MOUNTAIN SPOTTED FEVER
ERYTHEMA MIGRANS: INITIAL MACULE ENLARGES TO FORM A BULL'S EYE LESION, TYPICALLY ON THE THIGH, GROIN, OR AXILLA
RASH BEGINS ON THE WRISTS AND ANKLES AND LATER ON THE PALMS AND SOLES, SPREADING CENTRIPETALLY TO THE TRUNK AND FACE
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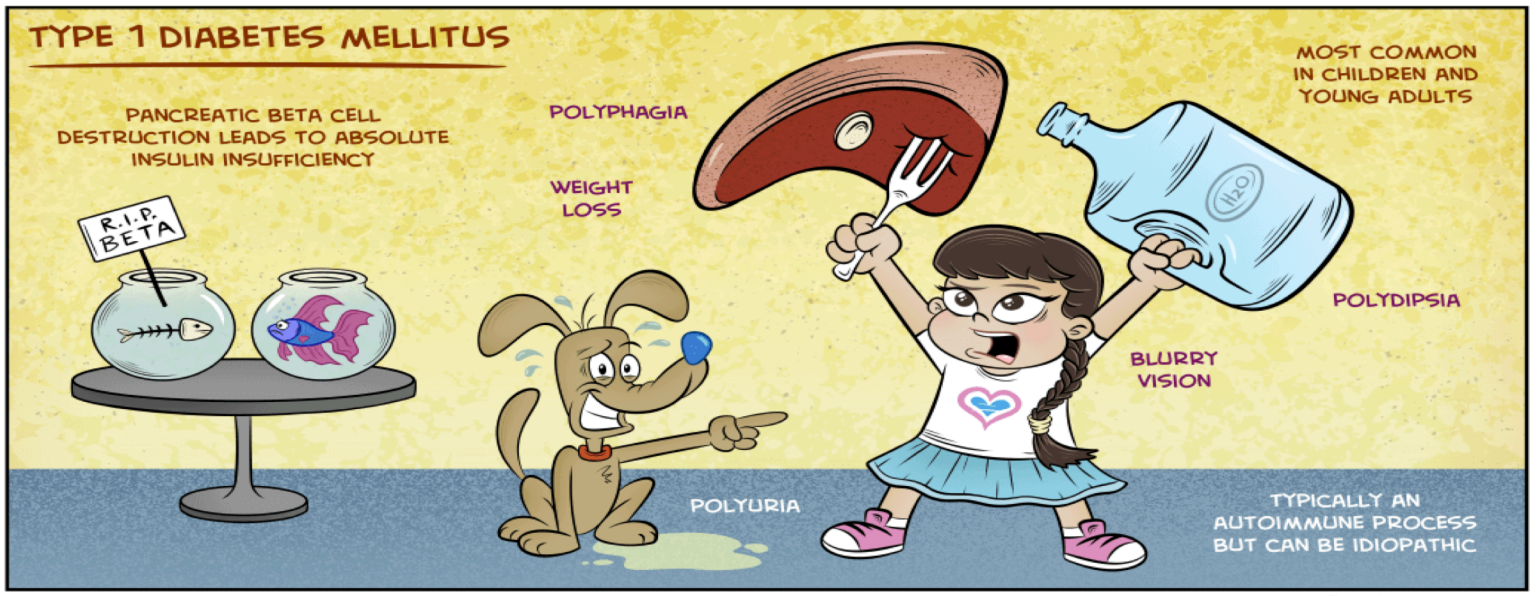
TYPE 1 DIABETES MELLITUS
PANCREATIC BETA CELL DESTRUCTION LEADS TO ABSOLUTE INSULIN INSUFFICIENCY
R.I.P. BETA
POLYPHAGIA
WEIGHT LOSS
MOST COMMON IN CHILDREN AND YOUNG ADULTS
H2O
POLYDIPSIA
BLURRY VISION
POLYURIA
TYPICALLY AN AUTOIMMUNE PROCESS BUT CAN BE IDIOPATHIC
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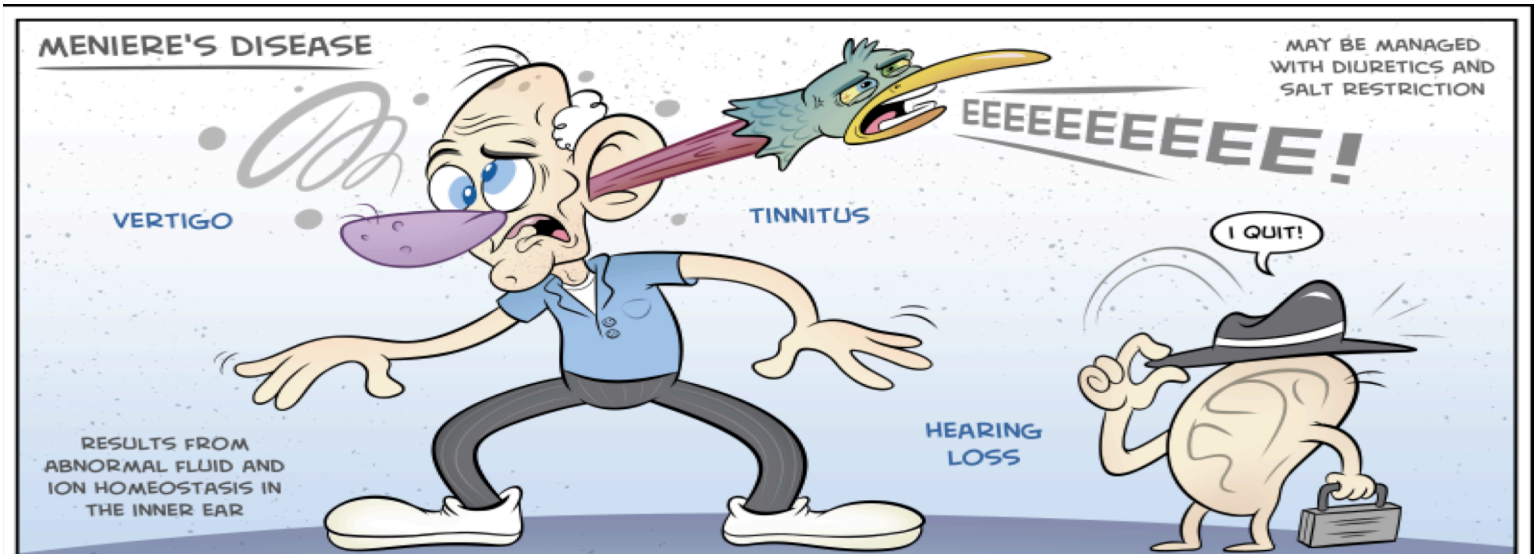
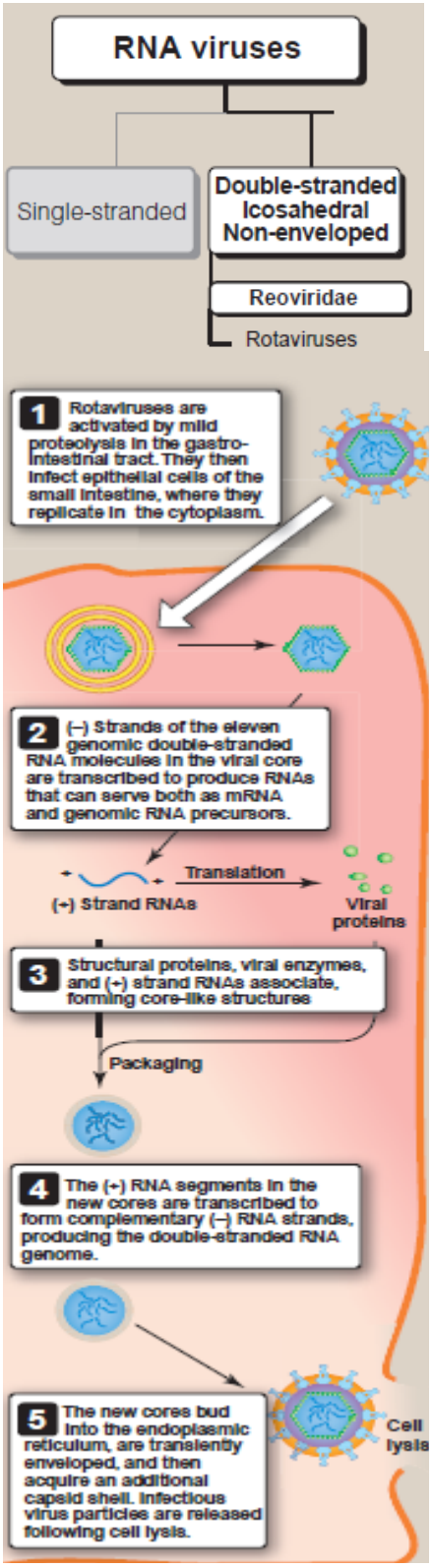

MENIERE'S DISEASE
MAY BE MANAGED WITH DIURETICS AND SALT RESTRICTION
EEEEEEEEEE!
VERTIGO
TINNITUS
I QUIT!
HEARING LOSS
RESULTS FROM ABNORMAL FLUID AND ION HOMEOSTASIS IN THE INNER EAR

CHAPTER 30

Double-stranded RNA Viruses: the Reoviridae

OVERVIEW:

The single genus in the family that is of medical importance is the genus Rotavirus, which causes severe viral gastroenteritis primarily in infants and young children. Viruses in the family Reoviridae are spherical, non-enveloped particles that have an icosahedral structure. The viral genome consists of ten to twelve segments of double-stranded (ds) RNA. The virions contain all the enzymes needed to make positive strand RNA transcripts, which are capped and methylated. Reoviruses replicate completely in the cytoplasm.



GENUS ROTAVIRUS:

Rotaviruses,found in many mammalian species, often have a fairly broad host range. Rotaviruses have a characteristic morphology that distinguishes them from other reoviruses; namely, they have the appearance of wheels with spokes radiating from the center and a smooth outer rim. The particles also have a large number of channels connecting the outer surface of the virion to the inner core. It has been suggested that these channels are involved in the import of substrates needed for RNA transcription and the extrusion of newly synthesized RNA transcripts.

A. Epidemiology:

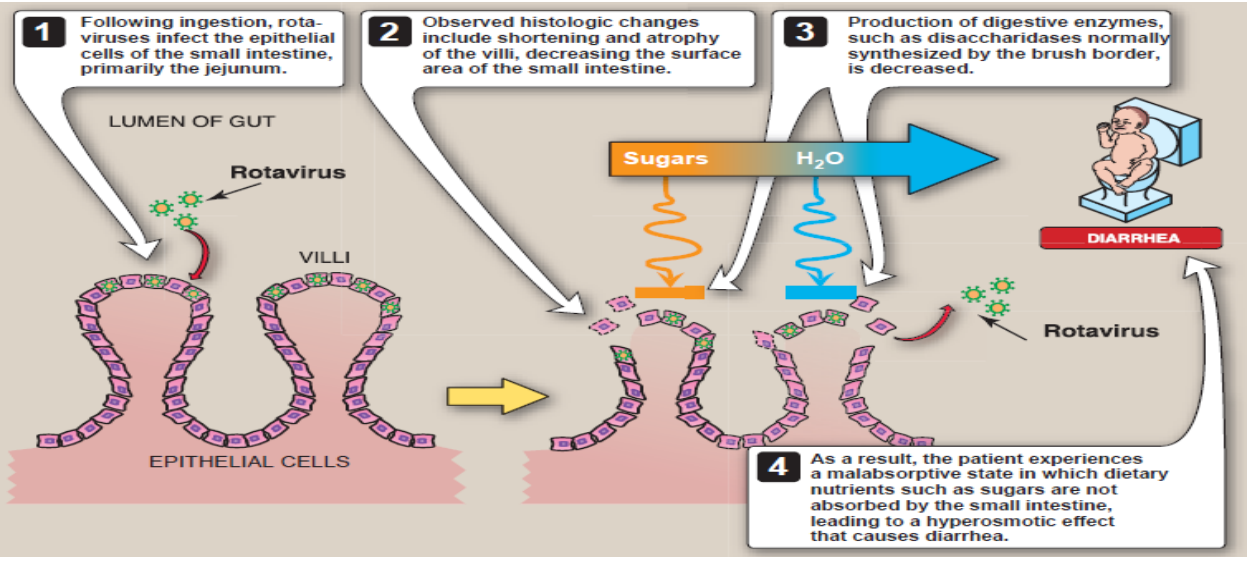
Rotaviruses are divided into seven serogroups of which group A is the most important cause of outbreaks of disease in humans. Transmission of rotaviruses is via the fecal–oral route. There is a marked seasonal incidence associated with rotavirus infections, with the peak months in the United States being January through March. Because infectious particles are relatively
stable, they can survive for extended periods on various surfaces.

B. Viral replication:

C. Clinical significance:

Following ingestion, rotaviruses infect the epithelial cells of the small intestine, primarily the jejunum. The incubation period is

usually 48 hours or less. Infection can be subclinical or may result in symptoms ranging from mild diarrhea and vomiting to severe, nonbloody, watery diarrhea with dehydration and loss of electrolytes. Although rotavirus infections are probably equally widespread around the world, the outcomes of infection vary significantly in different regions of the world. Despite the fact that more than ninety percent of children in the United States may have antibodies to rotaviruses by the age of three or four, mortality is low because patients who are severely ill are generally hospitalized, with fluid and electrolyte losses rapidly corrected.



D. Laboratory identification:

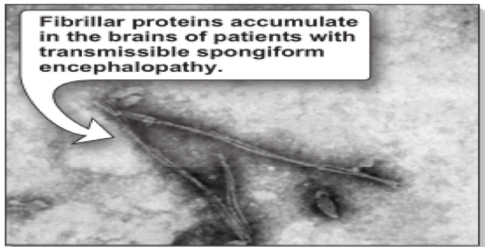
Severe diarrhea, dehydration, and electrolyte loss can be due to a variety of causes. Accordingly, a definitive diagnosis cannot be made on clinical grounds alone. As with many other viral infections, identification can be made by using an ELISA test or recognition of an increase in the titer of antiviral antibody in a patient's serum. Electron microscopy of stool specimens, although not a routine diagnostic measure, can aid in the identification of the virus because rotaviruses have a distinctive appearance.

E. Treatment and prevention:

There is no specific antiviral drug appropriate for treatment of rotavirus infections. The most important clinical intervention is the rapid and efficient replacement of fluids and electrolytes, usually intravenously. Formulations are also being produced that can be used in developing countries so that fluids and electrolytes can be replaced orally. Two new oral vaccines using weakened live virus have been shown to be highly efficacious in protecting infants against severe rotavirus gastroenteritis and not associated with increased risk of intussusception (telescoping of one portion of the intestine into another). Prevention of rotavirus infections requires improved sanitation measures.

CHAPTER 31

Unconventional infectious agent



I. **spongiform encephalopathies** prion is the causative agent characterized by absence of inflammatory signs, occure in humans are designated as kuru Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome,& fatal familial insomnia Histologically, these diseases are characterized by spongiform vacuolation of neuronal processes and gray matter accumulation of a unique protein

II.PRIONS is resistant to proteolytic degradation, form insoluble aggregates of fibrils when it's infectious

A. Presence of prion protein in normal mammalian brain[46]

A noninfectious form of prp , having the same amino acid and gene sequences as the infectious agent , specific mutational changes of single amino acids at a few sites appear to be the probability for exogenous infection & spontaneous conversion of the normal Piron protein to the infectious form[47]

B. Epidemiology

1. **Bovine spongiform encephalopathy**[48] caused by their feed processed with animal parts prepared from diseased sheep & cattle , the incubation time for symptoms to appear varies from 4 to 40 years, caused is unknown
2. **Kuru**[49] is human to human transmission ,Infection occurs by inoculation through breaks in the skin.
3. **Creutzfeldt-Jakob disease**[50] transmission by use of prion-contaminated human pituitary–derived growth hormone[51], corneal transplants implantation of

---

[46] *Present in normal mammalian brains on the surface of neurons and glial cells, It is referred to as cellular prion protein*

[47] *To become infectious lies in the conformation of the α-helices present in noninfectious are replaced by β-sheets in the infectious form leads to resistance for proteolytic degradation*

[48] *Called mad cow disease*

[49] *Acquired by an individual's exposure to diseased brain tissue in the course of ritualistic cannibalism , With cannibalism cessation the disease is disappear*

[50] *Sporadic and have an unknown etiology*

contaminated brain electrodes, & blood transfusions or inherited as a mutation in the PrP gene

C. Pathology

Exposure to prions results in multiplication of prion agents in the follicular dendritic cells within lymphoid tissues and in the spleen[52],

diseased brain tissue is characterized by accumulation of abnormal prion protein in the form of amyloid fibrils in neuron cytoplasmic vesicles& in the form of extracellular amyloid plaques, extensive vacuolation

within neurons, neuronal loss, & astroglial proliferation, destruction results in the spongiform appearance of gray matter[53] TSE[54] amyloid plaques

are morphologically similar to those of Alzheimer disease[55]

D. Clinical significance

1. Molecular basis of inherited TSEs [56] spontaneously occur , single amino acid substitutions or insertions of nucleotide repeat sequences are found in the PrP gene ,abnormal PrP^{Sc} acquires both the ability to "multiply," as well as the properties of an infectious agent

2. Major symptoms involve deposition of the PrP^{Sc} protein, most prominent features of CJD[57] are rapidly progressive dementia and behavioral disturbances, ending in death within 1 year , In GSS[58], ataxia is the more prominent feature, with death resulting in 2 to 6 years FFI[59], fatal within 1 year, has the uncontrollable insomnia

E. Laboratory identification

Presence of infectious PrP ^{Sc} in peripheral lymphatic tissue ,Conversion from the wild-type PrP^{C} protein to the abnormal PrP^{Sc} is associated with changes in iron homeostasis within the host[60]

F. Treatment and prevention

No treatment is currently available , prevention for decontamination of a CJD brain specimen are autoclaving at 132^{o} C, plus immersion in either undiluted sodium hypochlorite or 1N sodium hydroxide, all animals showing signs of illness are destroyed.

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[51] *Prepared from individuals who died from CJD*
[52] *But it is invade the central nervous system that results in the typical clinical effects*
[53] *In histologic section*
[54] *Transmissible spongiform encephalopathies*
[55] *the PrP gene is located on a different chromosome than the gene for the Alzheimer amyloid-β-protein precursor& there is no nucleotide or amino acid homology between the two*
[56] *Thought to increase greatly(10^{6}fold) the probability of transition to the infectious conformation*
[57] *Creutzfeldt-Jakob disease*
[58] *Gerstmann-Straussler syndrome*
[59] *fatalfamilial insomnia*
[60] *leading to the hypothesis that iron-binding proteins could be used as a biomarker*

CHAPTER 32

BACTERIA

Microorganisms	Diseases
Bacillus species Bacillus anthracis	Cutaneous anthrax Pulmonary anthrax ("wool-sorter's disease") Gastrointestinal form of anthrax
Bordetella species Bordetella pertussis	Pertussis ("whooping cough")
Borrelia species Borrelia burgdorferi	Lyme disease
Brucella species Brucella abortus Brucella canis Brucella melitensis Brucella suis	Brucellosis (undulant fever)
Campylobacter species Campylobacter jejuni	Acute enteritis
Chlamydia species Chlamydia pneumonia --- Chlamydia psittaci --- Chlamydia trachomatis	Community-acquired respiratory infection -- Psittacosis (ornithosis) -- Nongonococcal urethritis (NGU) Trachoma Inclusion conjunctivitis of the newborn (ICN) Lymphogranuloma venereum (LGV)
Clostridia species Clostridium botulinum -- Clostridium difficile -- Clostridium perfringens Clostridium tetani	Botulism (food poisoning) and floppy baby syndrome Pseudomembranous colitis -- Myonecrosis (gas gangrene) Acute food poisoning Anaerobic cellulitis Tetanus
Corynebacterium Corynebacterium diphtheriae	Diphtheria
Enterococcus species	Nosocomial infections

Enterococcus faecalis **Enterococcus faecium**	
Escherichia species **Escherichia coli**	**Urinary tract infections (UTI)** **Diarrhea** **-Enterotoxigenic E. coli (ETEC): This organism is a common cause of traveler's diarrhea** **-Enteropathogenic E. coli (EPEC) This organism is an important cause of diarrhea in infants** **-Enterohemorrhagic E. coli (EHEC): cause hemorrhagic colitis) (hemolytic uremic syndrome** **Meningitis in infants**
Francisella species **Francisella tularensis**	**Tularemia**
Haemophilus species **Haemophilus influenzae**	**Bacterial meningitis** **Upper respiratory tract infections , Pneumonia**
Helicobacter species **Helicobacter pylori**	**Acute gastritis** **Gastric carcinoma** **Gastric B cell lynphoma**
Legionella species **Legionella pneumophila**	**Legionnaires' disease** **Pontiac fever**
Leptospira species **Leptospira interrogans**	**Leptospirosis also known as (infectious jaudence, marsh fever, Weil's disease, swineherd's disease)**
Listeria species **Listeria monocytogenes**	**Listeriosis**
Mycobacterium species **Mycobacterium leprae** **Mycobacterium tuberculosis**	**Hansen disease (leprosy)** **Tuberculosis**
Mycoplasma species **Mycoplasma pneumoniae**	**Primary atypical pneumonia**
Neisseria species **Neisseria gonorrhoeae** **Neisseria meningitides**	**Gonorrhea complicated to (gonococcal salpingitis, pelvic inflammatory disease)** **Ophthalmia neonatorum** **Septic arthritis** **--** **Meningitis** **Waterhouse-Friderichsen syndrome**
Pseudomonas species **Pseudomonas aeruginosa**	**Localized infections such as (eye, ear, skin urinary tract , respiratory tract, gastrointestinal tract, central nervous system)** **Systemic infection such as (gastrointestinal tract, bacteremia, secondary pneumonia , endocarditis, bone and joint infections)**
Rickettsia species **Rickettsia rickettsii**	**Rocky Mountain spotted fever**
Salmonella species **Salmonella enterica serovar Typhi** **----** **Salmonella enterica serovar Typhimurium**	**Enteric (typhoid) fever** **Enterocolitis (gastroenteritis, foodborne infection)**

Shigella species Shigella sonnei Shigella dysenteriae Shigella flexneri Shigella boydii	Bacillary dysentery (shigellosis)
Staphylococcus species Staphylococcus aureus	Localized skin infections : a-superficial abscesses e.g sty b-subcutaneous abscesses e.g furuncles or boils c- deeper infection e.g carbuncles Diffuse skin infection—impetigo (pyoderma) Deep, localized infections Osteomyelitis,acute endocarditis, septicemia, and severe, necrotizing pneumonia Toxinoses toxic shock syndrome, gastroenteritis, scalded skin syndrome (bullous impetigo)
Staphylococcus epidermidis --- Staphylococcus saprophyticus	. Important cause of infections from prosthetic implants Cystitis in women
Streptococcus species Streptococcus agalactiae -- Streptococcus pneumonia --- Streptococcus pyogenes	Meningitis and septicemia in neonates Infections of adults such as (endometritis, pneumonia) Acute bacterial pneumonia Otitis media Meningitis Acute pharyngitis, or pharyngotonsillitis (scarlet fever) Acute rheumatic fever Impetigo Erysipelas Puerperal sepsis Invasive group A streptococcal (GAS) disease
Treponema species Treponema pallidum	Syphilis Congenital syphilis
Vibrio species Vibrio cholerae	Cholera
Yersinia species Yersinia pestis	Bubonic (septicemic) plague Pneumonic plague

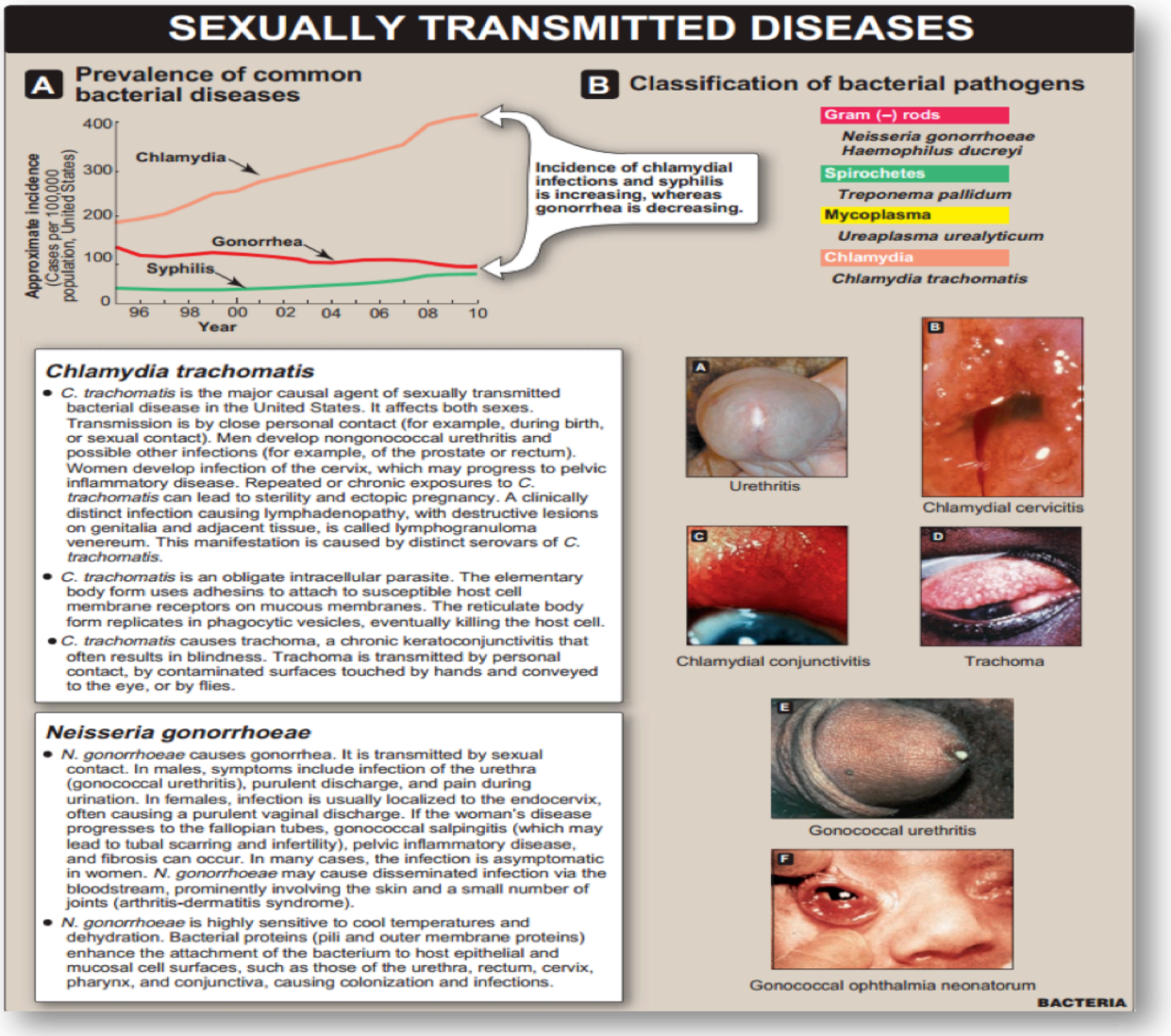
VIRUSES

Adenoviridae Adenoviruses	**Respiratory tract diseases** **Ocular diseases** **Gastrointestinal diseases**
Flaviviridae **Hepatitis C viruses**	**Hepatitis C**
Hepadnaviridae **Hepatitis B virus**	**Acute hepatitis** **Fulminant hepatitis** **Primary hepatocellular carcinomas (HCC; hepatomas)**
Herpesviridae **Epstein-Barr virus** **----------** **Herpes simplex virus, type 1** **----------** **Herpes simplex virus, type 2** **----------** **Human cytomegalovirus** **Varicella-zoster virus**	**Infectious mononucleosis (IM)** **Burkitt lymphoma , nasopharyngeal carcinoma, hodgkin disease** **----------** **Primary HSV-1 infections** **Latent HSV-1 infections** **(Upper part of the body)** **--** **Primary HSV-2 infections** **Latent HSV-2 infections** **(lower part of the body)** **HCMV infectious mononucleosis** **Cytomegalic inclusion disease** **HCMV infection of immunosuppressed transplant recipients** **HCMV infection of AIDS patients** **Varicella ("chickenpox")** **Zoster ("shingles")**
Orthomyxoviridae **Influenza virus**	**Influenza "flu"** **Reye syndrome**
Papovaviridae **Papillomavirus**	**Cervical carcinoma**
Paramyxoviridae **Measles virus** **Mumps virus** **Parainfluenza virus** **Respiratory syncytial virus**	**Measles** **Mumps** **Respiratory tract infections (croup, pneumonia, bronchiolitis , common cold)**
Picornaviridae **Coxsackievirus** **Hepatitis A virus** **Poliovirus**	**Coxsackievirus infections (upper respiratory tract infection, meningitis, gastroenteritis, herpanina, pleurisy, pericarditis, myocarditis, myositis)** **Hepatitis A (“infectious hepatitis”)** **Poliomyelitis**
Retroviridae **Human immunodeficiency virus**	**Acquired immune deficiency syndrome (AIDS** **HIV iinfection**
Rhabdoviridae **Rabies virus**	**Rabies**
Togaviridae **Rubella virus**	**German measles** **Congenital rubella**

CHAPTER 33

Disease Summaries

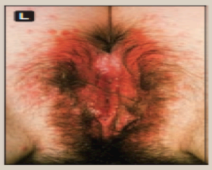
SEXUALLY TRANSMITTED DISEASES:



SEXUALLY TRANSMITTED DISEASES

Candida albicans

- *C. albicans* is a yeast that is part of the normal body flora, which can be found in the skin, mouth, vagina, and intestines. It can also be introduced to the body, for example, during sexual contact. Overgrowth of candida (candidiasis) occurs when competing bacterial flora are eliminated, for example, by antibacterial antibiotics. Unlike *Trichomonas vaginalis*, which requires that the vagina have a pH of about 6.0 for growth, *C. albicans* grows at the normal vaginal pH of 4.0.
- **Vulvovaginal candidiasis** is a common clinical syndrome, often seen both in the physician's office and at sexually transmiteed disease clinics. This syndrome causes itching and burning pain of the vulva and vagina, accompanied by a white discharge that is usually thick and curd-like.

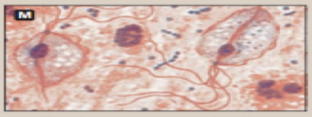


Vulvovaginal candidiasis

FUNGUS

Trichomonas vaginalis

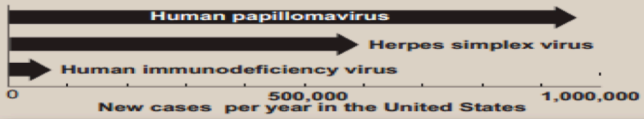
- *T. vaginalis* causes trichomoniasis, the most common protozoal urogenital tract infection of humans. The disease is largely sexually transmitted. In females, it causes inflammation of the mucosal tissue of the vagina, vulva, and cervix, accompanied by a copious, yellowish discharge. Less commonly, it infects the male urethra, prostate, and seminal vesicles, producing a white discharge.
- The optimum pH for growth of *T. vaginalis* is about 6.0; therefore, the organism does not thrive in the normal, acidic vagina, which has a pH of about 4.0. Abnormal alkalinity of the vagina favors acquisition of the disease.



Trichomonas vaginalis

PROTOZOAN

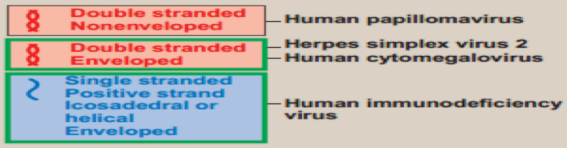
A Prevalence of common viral diseases



Herpes simplex virus type 2 (HSV-2)

- HSV-2 transmission generally occurs by sexual contact or by infection during birth. The sexually transmitted infection causes genital tract lesions, most of which are asymptomatic. When symptomatic, local pain and itching and systemic symptoms of fever, malaise, and myalgias may occur. Vesiculoulcerative lesions on the vulva, cervix, and vagina, or the penis, can be painful. Neonatal herpes is contracted by a baby during birth. If untreated, a disseminated infection results, often involving the CNS, leading to a high mortality rate.
- HSV-2 has a relatively rapid, cytocidal growth cycle that establishes latency in nerve ganglia. Reactivation of HSV-2 genital infection occurs frequently and is often asymptomatic. The infected person sheds virus during the reactivation period regardless of symptoms and can transmit the virus to a sexual partner during that period.

B Classification of viral pathogens



Herpes simplex lesions

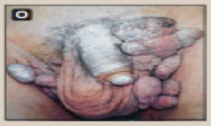
VIRUSES

SEXUALLY TRANSMITTED DISEASES

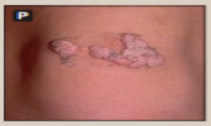
VIRUSES

Human papillomavirus (HPV)

- Infection by certain HPV causes anogenital warts (condylomata acuminata) verruca vulgaris. Transmission is through sexual contact or from mother to baby during birth.
- Lesions appear around the external genitalia, on the cervix, and/or inside the urethra or vagina, 4 to 6 weeks after infection. Some HPV infections are benign, but several types have been implicated as causes of different types of cancer, including cervical, rectal, penile, and oropharyngeal.



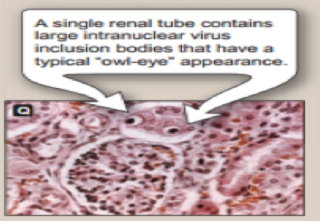
Condyloma acuminatum



Verruca vulgaris (on a finger)

Human cytomegalovirus (HCMV)

- HCMV is the most common intrauterine viral infection. It is also the most common viral infection of neonates. HCMV is transmitted by infected individuals through tears, urine, saliva, semen or vaginal secretions, and breast milk. Of infants born to women experiencing their first HCMV infection during pregnancy, 35 percent to 50 percent will become infected, of which 10 percent will be symptomatic (cytomegalic inclusion disease). Manifestations of the latter can include various degrees of damage to liver, spleen, blood-forming organs, and components of the nervous system (a common cause of hearing loss and mental retardation) or fetal death. Invasive opportunistic HCMV infections are common in AIDS patients. Such infections are also a danger to transplant recipients and other immunocompromised individuals.
- HCMV replicates initially in epithelial cells, usually of the respiratory and gastrointestinal tracts. This is followed by viremia and infection of all organs of the body. Latency is established in non-neural tissues, primarily lymphoreticular cells and glandular tissues.



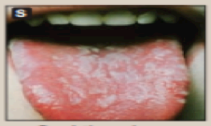
Cytomegalovirus infection. Section of kidney taken at autopsy from a 3-month-old boy.

Human immunodeficiency virus

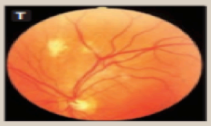
- HIV infects CD4+ T-cells, T cell precursors, and cells of the monocyte/macrophage lineage, resulting in a state of immunodeficiency. Transmission of HIV occurs by three routes: 1) sexually (virus is present in both semen and vaginal secretions); 2) via blood or blood products; and 3) perinatally (vertically). Several weeks after the initial infection, some individuals experience symptoms similar to infectious mononucleosis. The acute-phase viremia resolves into a clinically asymptomatic latent period lasting from months to many years. The progression from asymptomatic infection to acquired immune deficiency syndrome occurs as a continuum of progressive clinical states. Infected cells of the monocyte/macrophage system transport the virus into other organs including the brain. Death usually occurs from opportunistic infections, such as those shown at right.
- HIV is a nononcogenic retrovirus. It binds to a surface CD4 molecule, located primarily on helper T cells. HIV enters the cell by fusion of the virus envelope with the plasma membrane, followed by reverse transcription. This results in formation of a molecule of double-stranded DNA that is integrated into a host cell chromosome. Progeny virus are produced continuously, and the process eventually kills the host cell.

Opportunistic Infections of AIDS

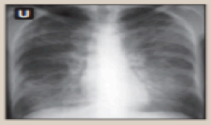
Cryptococcus present in the cerebrospinal fluid.



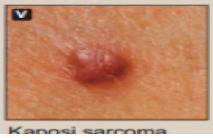
Oral thrush, or candidiasis



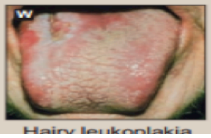
Cytomegalovirus retinitis



Pneumocystis pneumonia



Kaposi sarcoma



Hairy leukoplakia

SEXUALLY TRANSMITTED DISEASES

VIRUSES

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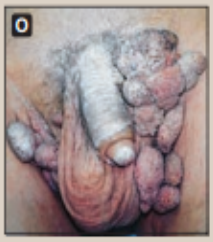

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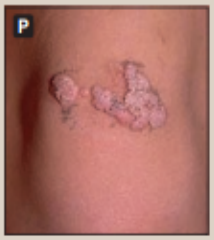

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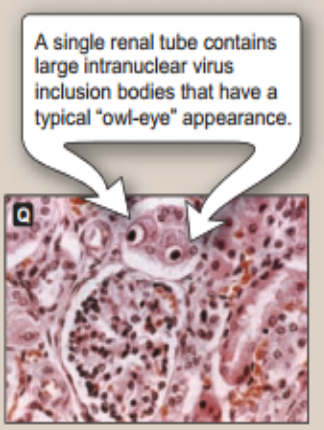

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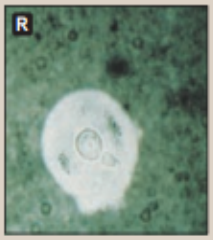

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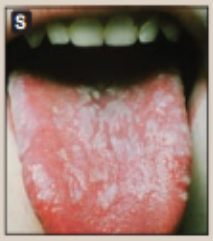

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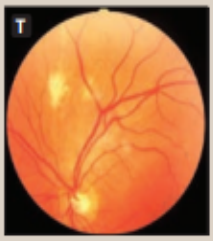

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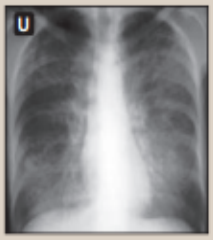

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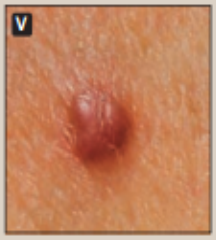
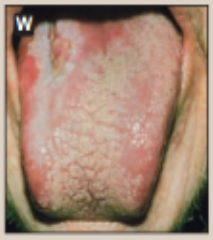




III. FOODBORNE ILLNESS (bacterial)

Foodborne illness results from eating food contaminated with organisms or toxins (Figure 33.3). is large social functions. These are commonly situations in which food may be left unrefrigerated or food preparation techniques are insufficiently safe. Foodborne illness often occurs from undercooked meats or dairy products that have remained at room temperature for extended periods. In patients with foodborne illness, fluid consumption is important to avoid dehydration. Children with diarrhea may be given an over-the-counter electrolyte product. Solid

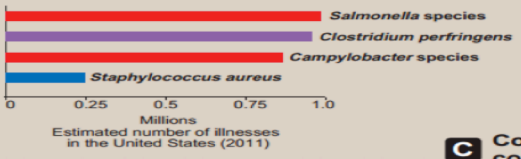
foods should not be eaten until the diarrhea has passed, and dairy should be avoided, as it can worsen diarrhea temporarily.

Intravenous fluid may be indicated in patients with severe diarrhea who are unable to drink fluids (for example, caused by nausea or vomiting)

Most patients spontaneously recover from the most common types of foodborne illnesswithin a couple of days. Antibiotic therapy is usually not indicated, except in cases of severe illness.

FOODBORNE ILLNESS (bacterial)

A Common causes of foodborne illness



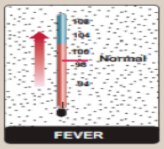
B Classification of pathogens

Gram (+) cocci
- *Staphylococcus aureus*

Gram (–) rods
- *Escherichia coli*
- *Campylobacter jejuni*
- *Salmonella* species
- *Shigella* species
- *Vibrio cholerae*

Anaerobic organisms
- *Clostridium botulinum*
- *Clostridium perfringens*

C Common complaints[1]



Salmonella species

- Nontyphoidal *Salmonella* serovars, particularly Typhimurium and Enteritidis, cause a localized gastroenteritis in which the symptoms result from causative bacteria proliferating in the intestine of affected individuals. Transmission is usually via food, especially chickens, eggs, and egg products.
- These organisms all invade host cells by injection of effector proteins directly into the host cytoplasm. Widespread antibiotic resistance among these organisms requires sensitivity testing to determine the appropriate antibiotic treatment, if any is given.

Clostridium species

- *Clostridium perfringens* is a major cause of food poisoning in the United States. The occurrence of clinical symptoms requires a large inoculum of 10^8 organisms or greater. Therefore, a typical episode of clostridial food poisoning involves cooking that fails to inactivate spores, followed by holding the food for several hours under conditions that allow bacterial germination and several cycles of growth.
- *Clostridium perfringens* secretes various exotoxins, enterotoxins, and hydrolytic enzymes that facilitate the disease process. Symptoms involved in clostridial food poisoning typically include nausea, abdominal cramps, and diarrhea, occurring 8 to 18 hours after eating contaminated food. Fever is absent and vomiting rare. The attack is usually self-limited, with recovery within 1 to 2 days.
- *Clostridium botulinum* causes botulism. A neurotoxin produced by the bacteria results in flaccid paralysis. Contact with the organism itself is not required, and hence, the disease is a pure intoxication.

Campylobacter jejuni

- *C. jejuni* is the leading cause of foodborne disease in the United States. It also causes traveler's diarrhea and pseudoappendicitis. *C. jejuni* is transmitted to humans primarily via the fecal–oral route—through direct contact, exposure to contaminated meat (especially poultry), or contaminated water supplies.
- *C. jejuni* infects the intestine, and it can cause ulcerative, inflammatory lesions in the jejunum, ileum, or colon. In otherwise healthy individuals, it typically causes an acute enteritis following a one- to seven-day incubation. The disease lasts days to several weeks, and generally is self-limiting. Symptoms may be both systemic (fever, headache, myalgia) and intestinal (abdominal cramping and diarrhea, which may or may not be bloody). Bacteremia may occur, most often in infants and older adults.

Staphylococcus aureus

- *S. aureus* gastroenteritis is caused by ingestion of food containing the bacterial enterotoxin. Often contaminated by a food-handler, these foods tend to be protein-rich and/or salty (for example, egg salad, cream pastry, or ham) and improperly refrigerated.
- The toxin stimulates the vomiting center in the brain by binding to neural receptors in the upper gastrointestinal tract. Symptoms such as nausea, vomiting, and diarrhea are acute following a short incubation period (less than 6 hours). The attack is usually self-limiting.

FOODBORNE ILLNESS (bacterial)

Shigella species

- *Shigella* species cause shigellosis (bacillary dysentery)—a human intestinal disease that occurs commonly among young children. Shigellae are typically spread from person to person, with food or water contaminated with fecal material serving as a major source of organisms.
- Shigellae invade and destroy the mucosa of the large intestine. The resulting bacillary dysentery is characterized by diarrhea with blood, mucus, and painful abdominal cramping. The disease is generally most severe in the very young and elderly, and among malnourished individuals, in whom shigellosis may lead to severe dehydration, and sometimes death.

Vibrio species

- *Vibrio cholerae* secretes a toxin which causes cholera, an infection in the small intestine. The cholera toxin causes an outflowing of ions and water to the lumen of the intestine. After an incubation period ranging from hours to a few days, profuse watery diarrhea ("rice-water" stools) begins. Untreated, death from severe dehydration causing hypovolemic shock may occur in hours to days, and the death rate may exceed 50 percent. Appropriate treatment reduces the death rate to less than 1 percent.
- Transmission occurs primarily by drinking water or eating food that has been contaminated by the feces of an infected person, including one with no apparent symptoms.
- Worldwide, cholera affects 3–5 million people and causes 100,000–130,000 deaths a year as of 2010. This occurs mainly in the developing world.

Escherichia coli

- *E. coli* is part of the normal flora of the colon, but pathogenic virotypes have acquired new virulence factors allowing them to be more pathogenic both inside and outside of the GI tract. Transmission of intestinal disease is commonly by the fecal-oral route, with contaminated food (such as beef and unpasteurized milk) and water serving as the vehicles.
- Several types of intestinal infections with *E. coli* have been identified. These differ in their pathogenic mechanisms. Among the most important are: 1) enterotoxigenic *E. coli* (ETEC)—a common cause of traveler's diarrhea in developing countries. ETEC colonizes the small intestine and produces enterotoxins. These cause prolonged hypersecretion of chloride ions and water by the intestinal mucosal cells while inhibiting the reabsorption of sodium, resulting in significant watery diarrhea over a period of several days. 2) Enterohemorrhagic *E. coli* (EHEC) binds to cells in the large intestine, where it produces an exotoxin (Shiga-like toxin) that destroys microvilli, causing a severe form of copious, bloody diarrhea (hemorrhagic colitis) in the absence of mucosal invasion or inflammation. Serotype O157:H7 is the most common strain of *E. coli* that produces Shiga-like toxin.

V. URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) most commonly affect either the lower urinary tract (infection of the urethra or bladder) or, less frequently, the upper urinary tract (acute pyleonephritis, or infection of the kidney). UTIs are termed “uncomplicated” when there is no underlying condition that increases the risk of infection, such as obstruction or urologic dysfunction. is one of the most common infections in the United States, especially in sexually active women.

Escherichia coli

is the most common cause of uncomplicated cystitis and pyelonephritis (70 to 95 percent of infections, Figure 33.4). Fecal contamination can lead to entry of an organism such as E. coli (one of the most common facultative organisms found in stool) into the urethra. These bacteria then move up into the bladder (and sometimes ascend into the kidney), producing infection. UTIs occur much more frequently in women as a result of the proximity of the urethral opening to the anus and the shorter length of the urethra before it opens into the bladder in women.

Staphylococcus saprophyticus as a causative agent

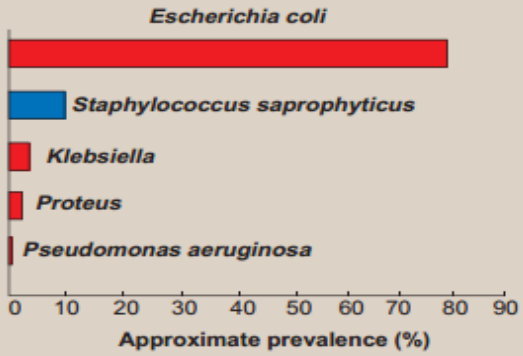
is a distant second to E. coli , causing 5 to 20 percent of infections. S. saprophyticus , although less common than E. coli , often presents as a more aggressive disease with approximately one half of the patients showing involvement in the upper urinary tract. These patients are also more likely to have recurrent infection.

Patients with uncomplicated UTI usually present with dysuria, urinary frequency, urinary urgency, and/or suprapubic pains. Pyuria (the production of urine that contains white blood cells) is commonly found in UTIs. Fever or flank tenderness could indicate pyelonephritis. If the features suggestive of vaginitis or urethritis described above are present, a pelvic examination and appropriate cultures should be performed.

The risk of UTI, both cystitis and pyelonephritis, can be increased by sexual intercourse

URINARY TRACT INFECTIONS

A Common causes of urinary tract infection (UTI)[1]



B Classification of pathogens

Gram (+) cocci

Staphylococcus saprophyticus

Gram (–) rods

Escherichia coli
Klebsiella species
Proteus species
Pseudomonas aeruginosa

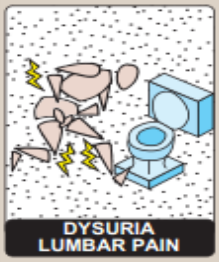
Escherichia coli

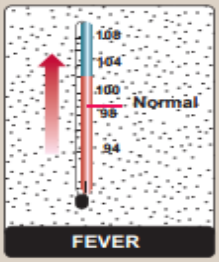
- *E. coli* is the most common cause of UTI, including cystitis and pyelonephritis. Women are particularly at risk for infection. Acquisition is frequently from the patient's flora.
- Uncomplicated cystitis (the most commonly encountered UTI) is caused by uropathogenic strains of *E. coli*, characterized by P fimbriae (an adherence factor). Complicated UTI (pyelonephritis) often occurs in settings of obstructed urinary flow, and may be caused by nonuropathogenic strains of *E. coli*. UTI requires treatment with antibiotics.

Staphylococcus saprophyticus

- *S. saprophyticus* is a frequent cause of cystitis in women, probably related to its occurrence as part of normal vaginal flora. It is also an important agent of hospital-acquired infections associated with the use of catheters.
- *S. saprophyticus* is a coagulase-negative staphylococcal species. It tends to be sensitive to most antibiotics, even penicillin G. It can be distinguished from most other coagulase-negative staphylococci by its natural resistance to novobiocin.

C Common complaints





Other enterobacteria

- Other genera of *Enterobacteriaceae*, such as *Klebsiella*, *Enterobacter*, *Proteus*, and *Serratia*, which can be found as normal inhabitants of the large intestine, include organisms that are primarily opportunistic and often nosocomial pathogens. They all frequently colonize hospitalized patients, especially in association with antibiotic treatment, indwelling catheters, or invasive procedures, causing extra-intestinal infections such as those of the urinary tract.
- Wide-spread antibiotic resistance among these organisms necessitates sensitivity testing to determine the appropriate antibiotic treatment.

Pseudomonas aeruginosa

- *P. aeruginosa* is a significant opportunistic pathogen and a major cause of hospital-acquired (nosocomial) infections such as UTI, particularly in patients who have been subjected to catheterization, instrumentation, surgery, or renal transplantation, or prior antibiotic therapy.
- *P. aeruginosa* disease begins with attachment and colonization of host tissue. Pili on the bacteria mediate adherence, and an alginate capsule reduces the effectiveness of normal clearance mechanisms. Host tissue damage facilitates adherence and colonization. Because *Pseudomonas* infections typically occur in patients with impaired defenses, aggressive antimicrobial therapy is generally required.

URINARY TRACT INFECTIONS

D Empiric therapy

Cystitis (uncomplicated)

- **Three days of therapy often sufficient**

1. **Ciprofloxacin**
2. **Trimethoprim/ sulfamethoxazole[1]**

Pyelonephritis

- **Ten to fourteen days of therapy often required**

1. **Amoxicillin/ clavulnate**
1. **Ciprofloxacin**
2. **Trimethoprim/ sulfamethoxazole**

V. MENINGITIS

Bacterial meningitis is a medical emergency that requires immediate diagnosis and treatment.

Virtually all patients with community-acquired bacterial meningitis show at least one of the classic triad of symptoms, which includes fever, neck stiffness, and altered mental status (Figure 33.5). These symptoms can develop over several hours, or they may take 1 to 2 days. Other symptoms may include nausea, vomiting, discomfort with bright lights, confusion, and sleepiness. Streptococcus pneumoniae and Neisseria meningitidis are responsible for 80% of all cases of bacterial meningitis.

Initial blood cultures are positive in 50 to 75 percent of adults with bacterial meningitis. A specimen of cerebrospinal fluid (CSF) should be obtained for cell count and differential, glucose and protein concentration, Gram stain, and culture. Characteristic findings in bacterial meningitis include decreased glucose concentration, elevated protein and white blood cell count in the CSF. Some patients may require computed tomography (CT) scan as a precaution before lumbar puncture.

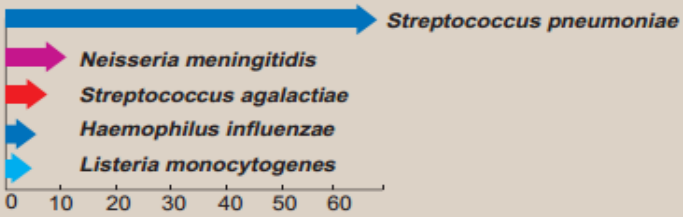
Therapy for bacterial meningitis requires bactericidal antimicrobial agents that can cross the blood–brain barrier into the CSF. Oral antibiotics should not be used because the dose and tissue levels tend to be considerably lower than with parenteral agents. Antibiotic therapy should be initiated immediately after lumbar puncture. If imaging is performed before lumbar puncture, therapy should be initiated before the patient is sent for neuroimaging. Delay in the initiation of antimicrobial therapy increases the risk of death or brain damage.

Most authorities recommend that an intravenous glucocorticoid such as dexamethasone be given immediately prior to or together with the first dose of antibiotic because of damage to the central nervous system caused by the inflammatory response to the infecting organism.

Initial therapy may be empiric with cefotaxime or ceftriaxone.

BACTERIAL MENINGITIS

A Overview of common causes of bacterial meningitis in adults[1]



B Classification of pathogens

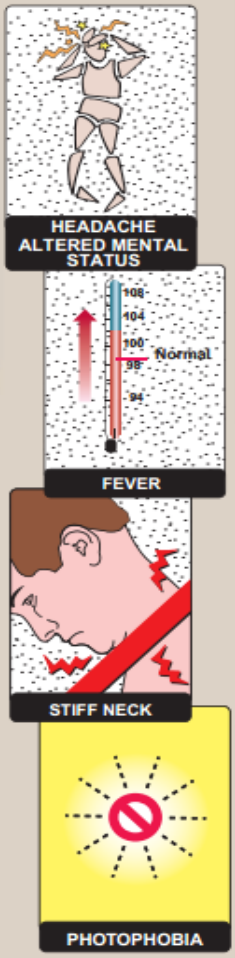
Gram (+) cocci
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

Gram (+) rods
- *Listeria monocytogenes*

Gram (–) cocci
- *Neisseria meningitidis*

Gram (–) rods
- *Haemophilus influenzae*

C Common complaints[2]



Streptococcus pneumoniae

- *S. pneumoniae* is an important cause of meningitis and pneumonia. It is carried in the nasopharynx of many healthy individuals. Infection can be either endogenous (in a carrier who develops impaired resistance to the organism) or exogenous (by droplets from the airway of a carrier).
- *S. pneumoniae* infections can result in a bacteremia leading to infection of several sites in the human body, including the central nervous system (CNS). This meningitis has a high mortality rate, even when treated appropriately. *S. pneumoniae* is the most common cause of bacterial meningitis in adults.

Neisseria meningitidis

- *N. meningitidis* is a common cause of meningitis. Transmission is via respiratory droplets. Pili allow the attachment of *N. meningitidis* to the nasopharyngeal mucosa.
- If meningococci penetrate the epithelial lining of the nasopharynx and enter the bloodstream, they rapidly multiply, causing meningococcemia. If *N. meningitidis* crosses the blood–brain barrier, it can infect the meninges, causing an acute inflammatory response that results in a purulent meningitis. The initial fever and malaise can rapidly evolve into severe headache, rigid neck, vomiting, and sensitivity to bright light. Coma can occur within a few hours. *N. meningitidis* is the most common cause of bacterial meningitis between the ages of 2 and 18 years.

Haemophilus influenzae

- *H. influenzae* is a normal resident of the human upper respiratory tract. Transmission is by respiratory droplets.
- After attaching to and colonizing the respiratory mucosa, the infection can become systemic, with bacteria spreading via the blood to the CNS. *H. influenzae* was a leading cause of bacterial meningitis, especially in infants and young children. A conjugated vaccine against *H. influenzae* capsular polysaccharide type b is now administered to infants and has dramatically lowered the number of meningitis cases attributable to this organism.

Streptococcus agalactiae

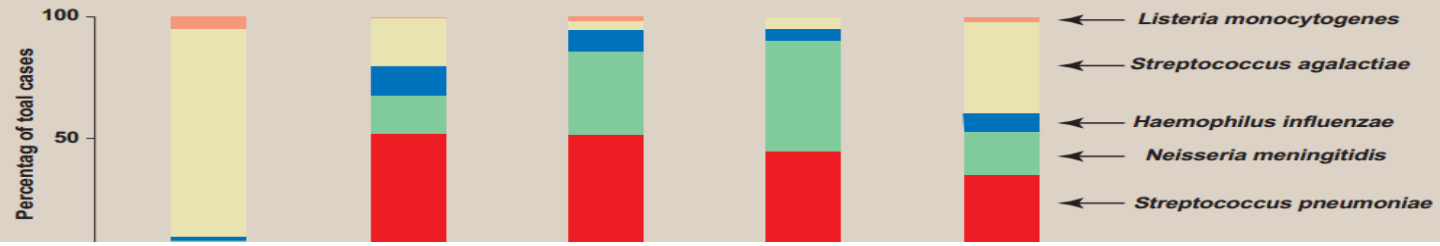
- *S. agalactiae* causes meningitis and septicemia in neonates. It is found normally in the genital tract of female carriers and the urethral mucous membranes of male carriers, as well as in the gastrointestinal (GI) tract (especially the rectum). Transmission occurs during birth and is sexually transmitted among adults.
- Infection of an infant occurs as it traverses the birth canal. *S. agalactiae* infection is a leading cause of neonatal meningitis, and it has a high mortality rate.

Listeria monocytogenes

- *L. monocytogenes* infections are most common among older adults, pregnant women, fetuses or newborns, and immunocompromised individuals. Meningitis is a common presentation. Listeria infections, which may occur as sporadic cases or in small epidemics, are usually foodborne, with the organism entering the body via the GI tract.

BACTERIAL MENINGITIS

D Approximate prevalence (%) in children (2003–2007)



Hepatitis

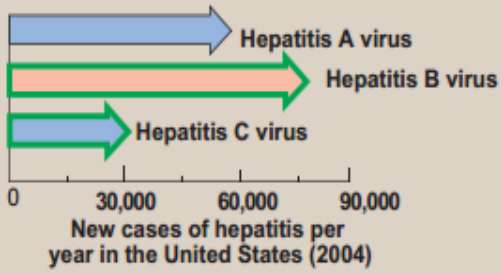
Hepatitis is inflammation of the liver. The disease can be caused by infections from parasites, bacteria, or viruses (such as hepatitis A, B, or C, as shown in Figure 33.6). Liver damage can also result from alcohol, drugs, or poisonous mushrooms. Hepatitis A, B, and C are clinically the most important forms of viral liver disease. Hepatitis A does not lead to chronic infection. Infection provides life-long immunity

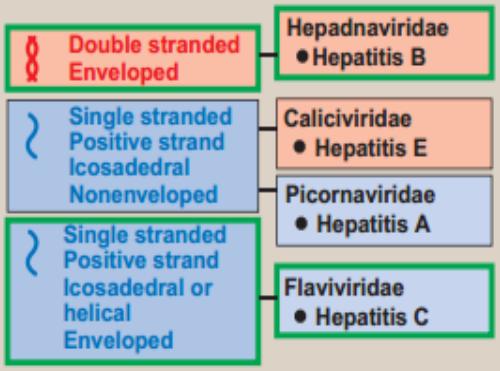
Persons at risk of hepatitis B infection include 1) individuals with multiple sex partners; 2) men who have sex with men; 3) sex contacts of infected persons; 4) injection drug users; and 4) household contacts of chronically infected persons. Death from chronic hepatitis B occurs in 15 to 25 percent of chronically infected persons.

Most hepatitis C infections result from illegal injection drug use. Transfusion-associated cases occurred prior to blood donor screening, but now the incidence is less than 1 per 2 million transfused units of blood. Fifty percent of those with hepatitis C go on to have chronic liver disease and, possibly, liver failure (cirrhosis) or liver cancer.

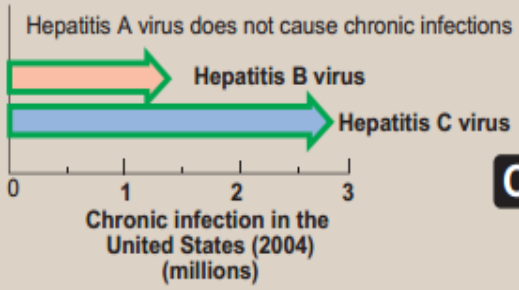
HEPATITIS

A New infections

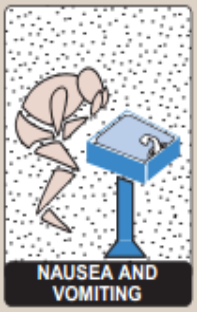


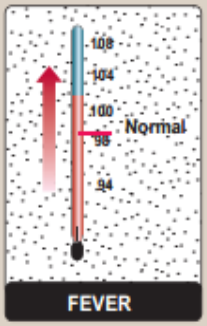


B Chronic infections



C Common complaints





Hepatitis A virus

- Hepatitis A virus (HAV) is a picornavirus, with a linear, single-stranded, positive-sense RNA genome. The virus is nonenveloped.
- Transmission is by the fecal–oral route. The main site of replication is the hepatocyte, where infection results in severe cytopathology, and liver function is severely impaired. The prognosis for patients with HAV is generally favorable, and development of persistent infection and chronic hepatitis is uncommon.
- Prevention of infection requires taking sanitary measures. Immune globulin has been used for many years, mainly as postexposure prophylaxis. A formalin-inactivated whole virus vaccine is available.

Hepatitis B virus

- Hepatitis B virus (HBV) is a hepadnavirus and the only human hepatitis virus that has a DNA genome. A unique feature of HBV is that the viral DNA replicates via an RNA intermediate. HBV is enveloped.
- Infectious HBV is present in all body fluids of an infected individual, including blood, semen, saliva, and breast milk. In the United States, HBV is most frequently contracted by adults through sexual intercourse or by intravenous (IV) drug use. In developing countries, it is transmitted primarily from mother to infant.
- The primary cause of hepatic cell destruction by HBV is the specific reaction of cytotoxic T lymphocytes with viral HBc and HBe antigens expressed on the infected cell's membrane. HBV infections can be acute (accompanied by mild fever, malaise, and myalgia, followed by jaundice and bilirubinuria, with an enlarged and tender liver) or chronic. Chronic carriers may be asymptomatic, but have a higher risk of developing severe chronic hepatitis, leading to progressive liver damage that may result in cirrhosis and/or hepatocellular carcinoma.
- A highly effective vaccine produced in genetically engineered cells is now available. It is included among routine childhood immunizations.

Hepatitis C virus

- Hepatitis C virus (HCV) is a member of the Flaviviridae. It has a linear, single-stranded, positive-sense RNA genome. HCV is enveloped.
- HCV was a major cause of post-transfusion hepatitis ("non-A, non-B"). IV drug users and patients on hemodialysis are also at high risk for infection with HCV. The virus can be transmitted sexually and from mother to infant.
- HCV replication occurs in hepatocytes and mononuclear cells. Both viral replication and the host immune response contribute to destruction of liver cells. Most infections are subclinical, but about 25 percent of infected individuals present with acute hepatitis, including jaundice. A significant proportion of infections progress to a chronic hepatitis and cirrhosis, and some of these individuals develop hepatocellular carcinoma. Coinfection with HBV is often present in those manifesting these more serious consequences. Combination treatment with ribavirin plus interferon provides a higher rate of success in eradicating viral infection in adults than does interferon alone.

HEPATITIS

Hepatitis D virus

- Hepatitis D virus (HDV, or delta agent) is found in nature only as a result of coinfection with HBV, and it requires HBV to serve as a helper virus for infectious HDV production. HDV has a circular, single-stranded negative-sense RNA genome and an envelope with a protein that is provided by HBV.
- HDV can be transmitted by the same routes as HBV. Pathologically, liver damage is essentially the same as in other viral hepatitides, but the presence of HDV usually results in more extensive and severe damage. No specific treatment for HDV infection is available.

Hepatitis E virus[1]

- Hepatitis E virus (HEV) is a calicivirus, with a linear, single-stranded, positive-sense RNA genome. HEV is non-enveloped.
- HEV is a major cause of enterically transmitted, waterborne hepatitis in developing countries.[1] The peak incidence is in young adults, and the disease is especially severe in pregnant women, in whom death can result from HEV infection.
- No antiviral treatment or vaccine is currently available.

	Drug	Vaccine
Hepatitis A	None	This inactivated virus vaccine offers 99 percent effective immunization against hepatitis A virus infection. Neutralizing antibodies persist for more than 3 years.
Hepatitis B	Lamivudine α-Interferon Adefovir Entecavir	Recombinant hepatitis B vaccine is a noninfectious subunit viral vaccine. The vaccine is derived from hepatitis B surface antigen (HBsAg) produced through recombinant DNA techniques. Following a three-dose series, immunity lasts approximately 5 to 7 years.
Hepatitis C	α-Interferon Ribavirin	None

Diseases of the eye:

Trachoma is the most prevalent eye infection in the world. However, physicians in developed countries are more likely to encounter patients with: 1) conjunctivitis (or pink eye), marked by pus or watery discharge and crust on the eyelashes; 2) styes, an abscess in the follicle of an eyelash; and 3) blepharitis, inflammation of the eyelids. Conjunctivitis is a condition which is often treated with antibiotics even though a minority of cases are caused by bacterial infection. Although it has characteristic signs, herpes simplex keratitis can be misdiagnosed as conjunctivitis.

Gonococcal eye infections are never treated topically and are always treated parenterally. Whether used for prophylaxis in an infant whose mother is known to have gonococcal cervicitis or for treatment of established gonococcal ophthalmia neonatorum, the CDC's recommendations are limited to IV or IM ceftriaxone. This is separate from the prophylactic use of erythromycin in the eyes of newborns regardless of the status of the mother, which is widely recommended and in many jurisdictions required by law.

Opportunistic infections of HIV:

Individuals with advanced human immunodeficiency virus (HIV) infection are vulnerable to infections and malignancies called "opportunistic infections" because they take advantage of the opportunity offered by a weakened immune system. The clinical symptoms of HIV infection are mainly caused by the emergence of opportunistic infections and cancers that the immune system would normally prevent. Infections that are rarely seen in those with normal immune systems are deadly to those with HIV.

Different opportunistic infections typically occur at different stages of HIV infection.

When the immune system is very weak due to advanced HIV disease, opportunistic infections such as Pneumocystis jiroveci, toxoplasmosis, and cryptococcosis develop. Many of the opportunistic infections that occur at this late stage can be fatal.

The development of highly active antiretroviral therapies (HAART) has greatly decreased the morbidity and mortality from HIV. HAART is effective in preventing opportunistic infections and should be considered for all HIV-infected persons.

However, certain patients are unable to take HAART, and others have not responded to HAART regimens. Such patients will benefit from prophylaxis against opportunistic infections. In addition, prophylaxis against specific opportunistic infections continues to provide survival benefits even among persons who are receiving HAART. With HAART, antimicrobial prophylaxis for opportunistic infections may not need to be lifelong.

Antiretroviral therapy can restore immune function. The period of susceptibility to opportunistic processes continues to be accurately indicated by CD4+ T-lymphocyte counts for patients receiving HAART. Stopping prophylactic regimens can simplify treatment, reduce toxicity and drug interactions, lower cost of care, and potentially facilitate adherence to

antiretroviral regimens.

BACTERIAL SINUSITIS:
Acute sinusitis is an infection of one or more of the paranasal (alongside the nose) sinuses. A viral infection accompanying the common cold is the most frequent cause of acute sinusitis. Viral infection is also the most common predisposing condition associated with acute bacterial sinusitis. However, only approximately 2 percent of viral sinusitis is complicated by acute bacterial sinusitis. There appear to be no signs and symptoms of acute respiratory illness that are both sensitive and specific in making the distinction between bacterial and viral infection.

Bacterial sinusitis is usually a self-limited disease, with 75 percent of cases resolving without treatment in one month. However, individuals with untreated acute bacterial sinusitis are at risk of developing intracranial and orbital complications as well as chronic sinus disease.

Viral sinusitis is associated with the presence of rhinovirus, parainfluenza, and influenza viruses in sinus aspirates. Other viruses which cause acute respiratory disease can also presumably produce viral sinusitis.

Sinusitis (Bacterial)
Common pathogens:
- Streptococcus pneumoniae
- Haemophilus influenza
- Staphylococcus aureus
- Anaerobes
- Moraxella catarrhalis

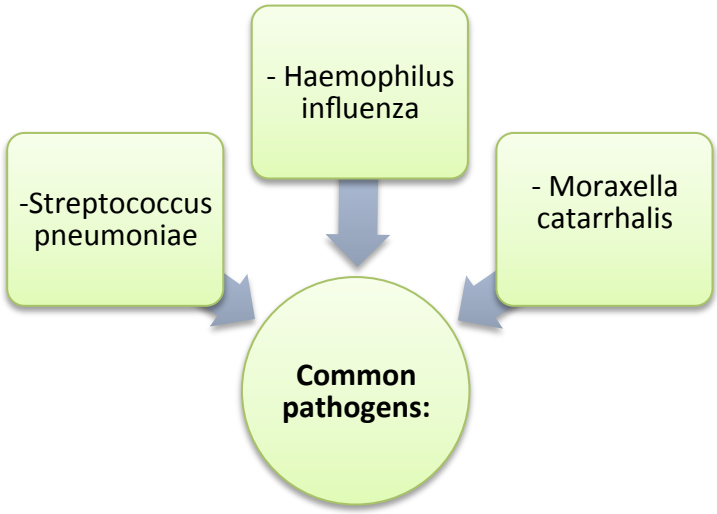
Common complaints:
- Nasal congestion
- Nasal discharge
- Cough
- Facial pain or pressure

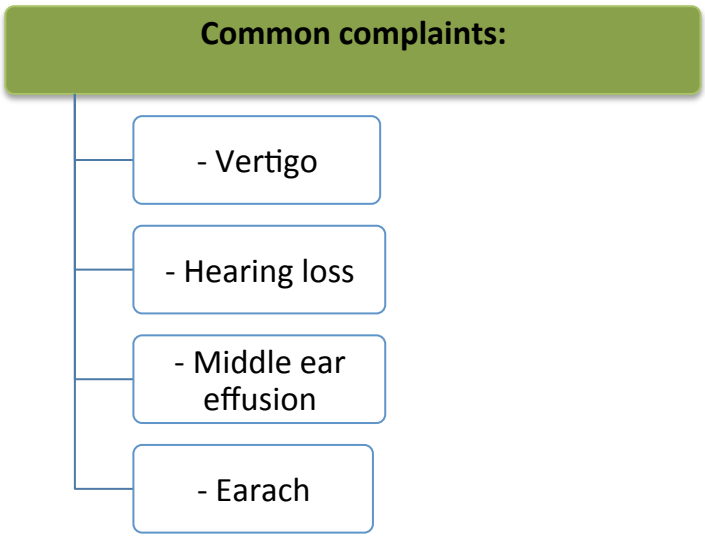
OTITIS MEDIA
Otitis media is one of the most frequent diagnoses in sick children visiting physicians' offices and accounts for almost one third of all antibiotic prescriptions for children in the United States.
Acute otitis media is characterized by the presence of fluid in the middle ear accompanied by acute signs of illness, and usually occurs in young children. Fluid may persist for weeks to months after the onset of signs of acute otitis media, despite appropriate therapy. Whenever fluid fills the middle ear space, there is some loss of hearing, which may lead to problems of development of speech, language, and cognitive abilities in the child.

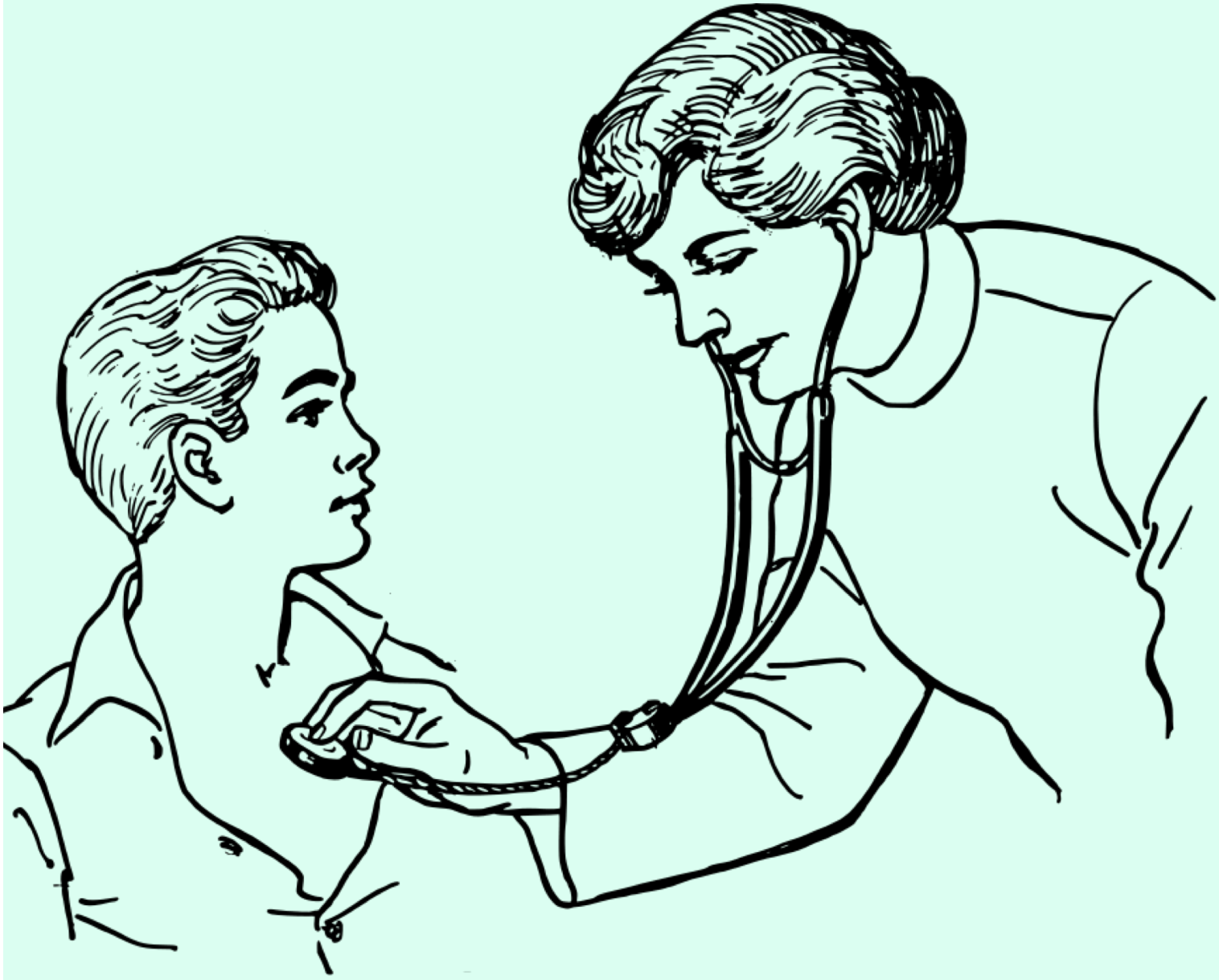
Otitis media often follows a upper respiratory tract viral infection or allergy that results in congestion of the respiratory mucosa of the nose, nasopharynx, and eustachian tube. Congestion of the mucosa in the eustachian tube causes an obstruction which can lead to accumulation of secretions produced by the mucosa of the middle ear. These secretions have

no way to exit and accumulate in the middle ear space. Viruses and bacteria that colonize the upper respiratory tract can reach the middle ear and may result in suppuration (formation of pus) with clinical signs of acute otitis media.

Otitis Media (Acute)







BEING A DOCTOR IS BEING KIND AND PROFFESSIONAL …

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