Anemias in children
Anemia...

... abnormal low hemoglobin, hematocrit or RBC count, lower than the age-adjusted reference range for healthy children.
Etiologic classification

I  Impaired red cell formation
   A/ Deficiency
      • Decreased dietary intake
      • Increased demand
      • Decreased absorption
      • Increased loss
   B/ Bone marrow failure
      • Failure of a single or all cell lines
      • Infiltration
   C/Dys hematopoietic anemia

II  Blood loss

III  Hemolytic anemia
    • Corpuscular (membrane, enzymatic or hemoglobin defects)
    • Extracorpusscular (immune, idiopathic)
Diagnosis of Anemia

- detailed history
- careful physical examination
- peripheral blood smear
  - red cell morphology
  - MCV
  - RDW (red cell distribution width)
  - WBC and platelet morphology

- Additionally:
  - bone marrow evaluation
  - additional testing
History

- Diet (iron, folate, vitB12 intake, onset of hemolysis after certain foods – e.g., fava beans)
- Family history (transfusion requirements of relatives, splenectomy, gallbladder disease)
- Environmental exposures (lead poisoning)
- Symptoms (headache, exertion dyspnea, fatigue, dizziness, weakness, mood or sleep disturbances, tinnitus)
- Melena, hematemesis, abdominal pain- chronic blood loss
Physical Examination

- Pallor
  (skin, oral mucosa, nail beds)
- Jaundice - hemolysis
- tachycardia
- tachypnea
- orthostatic hypotension
- venous hum
- systolic ejection murmur
- peripheral edema?
- Splenomegaly?
- Hepatomegaly?
- Glossitis?
- gingival pigmentation?
- Adenopathy?
- Facial, extremity examination
Peripheral Blood Components

important! Different values dependent on age!

- RBC
- Hgb
- HCT
- MCV – 80 – 100 fl/L (a calculated value)
- MCH
- RDW
- Reticulocyte Count
MCV for Characterize Anemia

Low (<70 fl)

*Hypochromic/Microcytic

- Iron deficiency anemia
- Thalassemia
- Sideroblastic anemia
- Chronic infection
- Lead poisoning
- Inborn errors of Fe metabolism
- Severe malnutrition
- Copper deficiency

(>85 fl)

*Macrocytic

- Normal newborn
- Increased erythropoiesis
- Post splenectomy
- Liver disease
- Aplastic anemia
- Megaloblastic anemia
- Down S.
- Obstructive jaundice
• Normocytic

- Acute blood loss
- Infection
- Renal failure
- Connective tissue disorders
- Liver disease
- Disseminated malignancy
- Early iron deficiency
- Aplastic anemia
- Bone marrow infiltration
- Dyserythropoietic anemia
Iron Deficiency Anemia

- **Causes**
  - Dietary deficiency
  - Increased demand (growth)
  - Impaired absorption
  - Blood loss (menstrual problems)

- **Symptoms**
  - GI: Anorexia, poor weight gain, pica, atrophic glossitis
  - CNS: fatigue, irritability
  - Cardiac: increased cardiac output, cardiac hypertrophy
  - Dry skin, thin hair, pallor, nail ridges
Iron Deficiency Anemia

*characteristics of peripheral blood smear
  – microcytic
  – hypochromic

*MCV and Hgb– decreased (Hgb<12g/L)
  – Ferritin – decreased (<13mg/dL)
  – TIBC - high

-Serum iron –decreased (N 50-150 µg/dL)
Iron Deficiency Anemia

• Treatment
  – oral iron supplementation: 4 - 6mg/kg/day of elemental iron
  – goal: to replace iron stores, not just circulating Hgb!
  – Reticulocytes- starts to rise in 3 -4 days,
  – Hbg- after 4- 5 days
  – After Hgb normalisation – continue Fe therapy 1-2 months to replace Fe stores
  – *Iron- rich foods:
    animal protein, green vegetables, iron fortified cereals
  – Folate, vit C
parenteral therapy (IM, IV)

– indications

• poor compliance
• severe bowel disease
• intolerance of oral iron
• chronic hemorrhage
• acute diarrhea disorder
Megaloblastic anemia

- Presence the megaloblasts in the bone marrow and macrocytes in the blood
- In > 95% occurs as a result of folate and vitamin B12 deficiency
- Deficiencies of ascorbic acid, tocopherol, thiamine may be related to megaloblastic anemia
- Dietary vitamin B12 (cobalamine) is required from animal sources (meat and milk)
Causes of vitamin B12 deficiency

I Inadequate dietary intake (<2mg/day) – malnutrition, veganism, maternal deficiency

II Defective vitamin B12 absorption
• Failure to secrete intrinsic factor
• Failure to absorption in small intestine

III Defective vitamin B12 transport

IV Disorders of vitamin B12 metabolism (congenital, acquired)
Folic acid deficiency

- One of the most common micronutrient deficiencies in the world (next to iron deficiency)
- Component of malnutrition and starvation
- Women are more frequently affected than men
- Folate sufficiency prevents neural tube defects
- Low mean daily folate intake is associated with twofold increased risk for preterm delivery and low infant birth weight
Causes of folic acid deficiency

- Inadequate intake (method of cooking, special diet, goat’ milk)
- Defective absorption (congenital or acquired)
- Increased requirements (rapid growth, chronic hemolytic anemia, dyserythropoietic anemias, malignant disease, hypermetabolic state, cirrosis, post –BMT)
- Disorders in folic acid metabolism (congenital, acquired)
- Increased excretion
Clinical features of cobalamine and folate deficiency

- Insidious onset: pallor, lethargy, fatigability, anorexia, sore red tongue and glossitis, diarrhea
- History: similarly affected sibling, maternal vitamin B12 deficiency or poor maternal diet
- Vitamin B12 deficiency: signs of neurodevelopmental delay, apathy, weakness, irritability, athetoid movements, hypotonia, peripheral neuropathy, spastic paresis
Diagnosis

- Red cell changes: Hgb usually reduced, *MCV increased to levels 110 – 140fl.*, MCHC normal,
- in blood smear many macrocytes and macro-ovalocytes, anisocytosis, poikilocytosis, presence of Cabot rings, Howell-Jolly bodies, punctate basophilia
- White blood cell count reduced to 1500 – 4000/mm³, neutrophils show *hypersegmentation* (>5 lobes)
- Platelets count moderately reduced (50,000 – 180,000/mm³)
- Bone marrow: megaloblastic appearance
- Serum vitamin B12 values lowered (normal 200 – 800 pg/ml)
- Serum and red cell folate levels – wide variation in normal range; less than 3 ng/ml - very low, 3-5 ng/ml - low, >5-6 ng/ml normal, in red cell: 74-640 ng/ml
- Schilling urinary excretion test – measurement of intrinsic factor availability and absorption of vitamin B12
Treatment

Vitamin B12 deficiency
Prevention in cases of risk of vitamin B12 deficiency
Treatment 25 – 100µg vitamin B12

Folic acid deficiency
   Correction of the foliate deficiency (100-200µg/day)
   Treatment of the underlying causative disorder
   Improvement of the diet to increase folate intake
Bone marrow failure
• Isolated quantitative failure of one cell line, a single cytopenia, e.g. erythroid, myeloid, megakaryocytic
• A failure of all three cell lines (pancytopenia with hypoplastic or aplastic bone marrow)
• A quantitative failure of the bone marrow, e.g. congenital dyserythropoietic anemia

• The invasion of the bone marrow by non-neoplastic or neoplastic condition
Diamond-Blackfan anemia
congenital pure red cell aplasia

The erythroid progenitor cell is intrinsically abnormal in the following aspects:

• Decreased sensitivity to erythropoietin (EPO)
• Decreased sensitivity to EPO not corrected by IL-3 and GM-CSF

caused by:

• Functional abnormalities in the erythropoietin receptors
• Erythroid progenitors are abnormally sensitive to a deprivation of erythropoietin, resulting in an accelerated rate of apoptosis
Clinical features

- Anemia and pallor in first 3 months, 35% is anemic at birth, 65% identified by 6 months of age and 90% by 1 year
- Platelets and white cell count – normal
- 25% have prenatal or postnatal growth failure and associated congenital defects, including short stature, abnormalities of thumbs, skeletal anomalies, congenital heart defects, webbed neck, urinary tract abnormalities and craniofacial dysmorphism
- Chromosomal studies generally normal
- No hepatosplenomegaly
- Malignant potential (increased incidence of ALL, AML, hepatocellular carcinoma)
Diagnosis

• Anemia and reticulocytopenia
• Bone marrow with virtual absence of normoblasts

Differential diagnosis

• Transient erythroblastopenia of childhood (TEC)
• Congenital hypoplastic anemia
Treatment

• Prednisone 2 mg/kg/day,
  when the hemoglobin level reaches 10.0 g/dl → dose reduction to minimum necessary
• Packed red cell transfusion, leukocyte–depleted
• Bone marrow transplantation in steroid–resistant, transfusion-dependent patients
Fanconi anemia
congenital aplastic anemia

- Rare inherited disorder, autosomal-recessive trait
- Pancytopenia: develops between 4 and 12 years of age
- It may present with isolated anemia or leukopenia or anemia + thrombocytopenia
- Macrocytosis (high MCV), high HbF, high erythropoetin, presence of i antigen – characteristic of stress erythropoiesis
- Diepoxybutane (DEB)-induced chromosomal breakages
- Hypocellularity and fatty replacement in bone marrow
- Congenital anomalies: patchy brown pigmentation of the skin, short stature, skeletal anomalies, hyperreflexia, hypogonitalism, microcephaly, microphthalmia, strabismus, ptosis, nystagmus, abnormalities of the ears, deafness, mental retardation, renal and cardiac anomalies
- Chromosomal breakages and structural abnormalities, chromatoid exchange
- High incidence of AML, carcinoma
Treatment:

Supportive:
- Packed red blood cells and platelets (irradiated, leukocyte reduced)
- Chelation treatment in iron overload
- Androgen therapy

Active:
- Allogenic bone marrow transplantation
Acquired aplastic anemia

Pathophysiology

- Immunologically mediated, tissue-specific, organ-destructive mechanism
- Exposition to an antigen $\rightarrow$ cells and cytokines of the immune system destroy stem cells in the marrow $\rightarrow$ pancytopenia
- Gamma–interferon plays a central role in the pathophysiology of AA
- T cells from AA patients secrete gamma-IFN and TNF – potent inhibitors of both early and late hematopoietic progenitor cells
- Cytotoxic T cells secrete also IL-2, which causes polyclonal expansion of the T cells
Causes of acquired AA

Idiopathic (70%)

Secondary:

- Drugs: cytostatics, antibiotics (sulfonamides, chloramphenicol), anticonvulsants (hydantoin), antirheumatics, antidiabetics, antimalarian
- Chemicals: insecticides
- Toxins: benzene, carbon tetrachloride, glue, toluene
- Irradiation
- Infections: viral (hepatitis A, B, C, HIV, EBV, CMV, parvovirus)
- Immunologic disorders: GvHD
- Preleukemia, MDS, thymoma
- Malnutrition
- Paroxysmal nocturnal hemoglobinuria
Severity

- **Severe AA**: bone marrow cellularity $<25\%$
  - Granulocyte count $<500/mm^3$
  - Platelet count $<20,000/mm^3$
  - Reticulocyte count $<40,000/mm^3$
- **Very severe AA**: granulocyte count $<200/mm^3$
Clinical findings:

- Anemia (pallor, easy fatigability, loss of appetite)
- Thrombocytopenia (petechiae, easy bruising, severe nosebleeds)
- Leukopenia (increased susceptibility to infections and oral ulcerations)
- Hyperplastic gingivitis
- No: hepatosplenomegaly and lymphadenopathy
Laboratory findings

- Anemia normocytic, normochromic
- Reticulocytopenia
- Leukopenia: granulocytopenia often < 1500/mm$^3$
- Thrombocytopenia: often < 30,000/mm$^3$
- Bone marrow: marked depression or absence hematopoietic cells and replacement by fatty tissue
- Normal chromosomol analysis
Treatment

Severe AA:

• Allogeneic BMT
• In the absence of availability of an HLA-matched sibling marrow donor - immunoablation (ATG, cyclosporine, methylprednisolone, growth factors- G-CSF)
Hemolytic anemia
Corpuscular defects

→ Membrane defects
→ Enzyme defects
→ Hemoglobin defects
→ Congenital dyserythropoietic anemias

Extracorpuscular defects

→ Immune
→ Nonimmune
Clinical features suggesting a hemolytic process

- Ethnic factors: incidence of sickle gene factor in the black population (8%), high incidence of thalassemia in people of Mediterranean ancestry, high incidence of glucose-6-phosphate dehydrogenase deficiency among Sephardic Jews
- Age factors: anemia and jaundice in an Rh+ infant born to a mother Rh- or a group A or group B infant born to a group 0 mother
- History of anemia, jaundice, or gallstones in family
- Persistent or recurrent anemia associated with reticulocytosis
- Anemia unresponsive to hematins
- Intermittent bouts or persistent indirect hyperbilirubinemia
- Splenomegaly
- Hemoglobinuria
- Presence of multiple gallstones
Corpuscular hemolytic anemias

Membrane defects

• Morphologic abnormalities: hereditary spherocytosis, elliptocytosis, stomatocytosis, acanthocytosis

• Spectrin is responsible for maintaining red cell shape, regulates the lateral mobility of integral membrane proteins and provides structural support for the lipid bilayer
Hereditary spherocytosis

Genetics
• Autosomal-dominant inheritance (75%), non-family history –25%
• Most common in people of northern European heritage
• Incidence of 1 in 5000

Pathogenesis
• Membrane instability due to dysfunction or deficiency of a red cell skeletal protein: **ankyrin** (75-90%) and/or **spectrin** (50%)
The sequelae are as follow:

- Sequestration of red cells in the spleen (due to erythrocyte deformability)
- Depletion of membrane lipid
- Decrease of membrane surface area relative to volume, resulting in a decrease in surface area-to-volume ratio
- Tendency to spherocytosis
- Influx and efflux of sodium increased; cell dehydration
- Increased glycolysis
- Premature red cell destruction
Hematology

- Anemia mild to moderate; in erythroblastopenic crisis Hb may drop to 2 – 3g/dl
- MCV usually decreased, MCHC raised
- Reticulocytosis
- Blood film – microspherocytos, hyperdense cells, polychromasia
- Coomb’s test negative
- Increased red cell osmotic fragility – spherocytes lyse in higher concentrations of saline than normal red cells, occasionally only demonstrated after incubation of blood sample at 37°C for 24 hours
- Autohemolysis at 24 and 48 hours increased, corrected by the addition of glucose
- Reduced red cell survival
- Marrow- normoblastic hyperplasia, increased iron
- EMA-test
Biochemistry

- Raised bilirubin, mainly indirect reacting
- Obstructive jaundice with increased direct-reacting bilirubin; may develop due to gallstones, a consequence of increased pigment excretion
Clinical features

• Anemia and jaundice- severity depends on rate of hemolysis, degree of compensation of anemia by reticulocytosis, and ability of liver to conjugate and excrete indirect hyperbilirubinemia
• Splenomegaly
• Presents in newborn (50% of cases) with hyperbilirubinemia, reticulocytosis, normoblastosis, spherocytosis, negative Coomb’s test, and splenomegaly
• Presence before puberty in most patients
• Sometimes diagnosis made much later in life by chance
Complications

• Hemolytic crisis – with pronounced jaundice due to accelerated hemolysis (may be precipitated by infection)
• Erythroblastopenic crisis – dramatic fall in Hb level and reticulocyte count, usually associated with parvovirus B19 infection
• Folate deficiency caused by increased red cell turnover, may lead to superimposed megaloblastic anemia
• Gallstones in 50% of untreated patients, incidence increases with age
• Rarely hemochromatosis
Treatment

- Folic acid supplement 1mg/day
- Leukocyte-depleted packed red cell transfusion for severe erythroblastopenic crisis
- Splenectomy for moderate to severe cases
Hereditary elliptocytosis (HE)

- Is due to various defects in the skeletal proteins, spectrin and protein 4.1, it results increased membrane rigidity and in decreased cellular deformability
- Autosomal-dominant mode of inheritance
- Elliptocytes varies from 50 to 90%
- Osmotic fragility normal or increased
- Treatment: transfusion, splenectomy, prophylactic folic acid
Another types of membrane defects

- Hereditary stomatocytosis
  (the cells contain high Na and low K concentrations)
- Hereditary acanthocytosis
- Hereditary xerocytosis
Enzyme defects

• **Pyruvate Kinase deficiency**: defective red cell glycolysis
  • Red cell rigid, deformed and metabolically and physically vulnerable
  • Autosomal – recessive inheritance
  • Nonspherocytic hemolytic anemia
  • Variable severity: moderate severe anemia
  • Neonatal jaundice
  • Splenomegaly
  • Gallstones, hemosiderosis, bone changes

Treatment: folic acid supplementation, transfusions, splenectomy
Glucose-6-Phosphate Dehydrogenase deficiency

• Sex-linked recessive mode of inheritance
• Disease fully expressed in hemizygous males and homozygous females
• Most frequent among blacks and those of Mediterranean origin
• Associations: hemolysis may be produced by drugs, fava (broad) bean, infections
Clinical features

Drug induced hemolysis:
- Analgetics and antipyretics
- Antimalarial agents
- Sulfonamides
- Nitrofurans
- Sulfones

Favism:
- acute life-threatening hemolysis often leading to acute renal failure caused by ingestion of fava beans
Associated with mediterranean and Canton varieties

Neonatal jaundice

Chronic nonspherocytic anemia

Treatment:
Avoid drugs deleterious in G6PD, splenectomy
Hemoglobin defects

→ Thalassemias
  • Alpha chains hemoglobinopathies:
    Deletion of two genes – alpha Thalassemia minor
  • Beta chain hemoglobinopathies (Hgb S, C, E, D)
    Beta Thalassemia Major (impaired beta chain synthesis)

→ Sickle Cell Disease: Hgb SS disease, Hgb S-C disease, Hgb S-beta
Sickle Cell Disease (SCD)

- Most common abnormal hemoglobin found in US (8% of the black population)
- at birth the incidence is 1 in 625

Genetics:
- transmitted as an incomplete autosomal-dominant trait
- Homozygotes (two abnormal genes) do not synthetize Hb A, red cell contain 90-100% Hb S
- Heterozygotes (one abnormal gene) have red cell containing 20-40% Hb S
Pathophysiology:

A single amino acid substitution: valine for glutaminic acid

( in the beta-polypeptide chain) →

• Different electrophoretic mobility
• HbS is less soluble than HbA
• Sickle cells are prematurely destroyed causing a hemolytic anemia
• Sickle cells result in increased blood viscosity and impaired blood flow and initiate thrombi
Clinical features

- Anemia - moderate to severe normochromic, normocytic
- Reticulocytosis
- Neutrophilia common
- Platelets often increased
- Blood smear: sickle cells, increased polychromasia, nucleated red cells, and target cells
- Erythrocyte sedimentation rate (ESR) – low
- Hemoglobin electrophoresis: HbS migrates slower than HbA, giving the diagnostic SS pattern
Crises

- Vaso-occlusive or symptomatic crisis:
  - hand–foot syndrome (dactylitis) – hand-foot swelling
  - bone crises - osteonecrosis
  - CNS crises - thrombosis/ bleeding
  - pulmonary crises - dyspnea, severe hypoxemia
  - priapism - hematuria,

- intrahepatic vasoocclusive crisis

- Splenic sequestration crisis due to of pooling large amount of blood in the spleen) – splenomegaly, abdominal pain of sudden onset

- Erythroblastopenic crisis (cessation of red cell production)

- Hyperhemolytic crisis, unusual, in association with certain drugs or acute infections
Organ dysfunction

- Central nervous system (acute infarction of the brain) – motor disabilities, seizures, speech defects, deficit in IQ
- Cardiovascular system (cardiomegaly, myocardial dysfunction)
- Lungs (reduced $\text{PaO}_2$, reduced saturation, increased pulmonary shunting, acute chest syndrome)
- Kidneys (increased renal flow, increased GFR, enlargement of kidneys, hyposthenuria, proteinuria, nephrotic syndrome)
- Liver and biliary system (hepatomegaly, cholelithiasis)
- Bones (dactylisis, avascular necrosis)
• Eyes (retinopathy, angioid streaks, hyphema – blood in anterior chamber))
• Ears (sensorineural hearing loss)
• Adenotonsillar hypertrophy
• Skin (cutaneous ulcers of the legs)
• Genitourinary (priapism)
• Growth and development (by 2 –6 years of age the height and weight delayed)
• Delayed sex maturation
• Functional hyposplenism (progressive fibrosis)
• Hemostatic changes (hypercoagulable state)
Diagnosis

- In utero: by PCR amplification of specific DNA sequences from fetal fibroblasts (obtained by amniocentesis)
- In newborn: electrophoresis for separation of hemoglobins

Management

- Comprehensive care (prevention of complications)
- Prophylaxis of infections pneumococcal vaccine, *H. Influenzae* vaccines, early diagnosis of infections
Treatment modalities

Antisicking therapy:

• fetal hemoglobin production stimulating agents (5-Azacytidine, hydroxyurea, recombinant EPO, short-chain organic acids)
• Red cell HbS concentration reducing agents (calcium channel blockers)
• Membrane active agents
• Hemoglobin solubility increasing agents
• Bone marrow transplantation
Thalassemias

Beta-thalassemia – impaired beta-chain production
Alpha-thalassemia – impaired alpha-chain production

Genetic defects:

• Two genes for Beta-globin synthesis (one on each chromosome 11)
  B-thalassemias are due to point mutations in one or both genes
• Four genes for a-globin synthesis (two on each chromosome 16)
  Most a-thalassemias are due to deletion of one or more a-genes
Hematology

- Hypochromic, microcytic anemia
- Reticulocytosis
- Leukopenia, thrombocytopenia
- Blood smear: target cells and nucleated cells, extreme anisocytosis, contracted red cells, polychromasia, punctate basophilia, circulating normoblasts
- HbF raised, HbA2 – increased
- Bone marrow: megaloblastic (due to folate depletion), erythroid hyperplasia
- Decreased osmotic fragility
- High serum ferritin

Biochemistry

- Raised bilirubin
- Evidence of liver dysfunction (late, as cirrhosis develops)
- Endocrine abnormalities (diabetes, hypogonadism)
Clinical features

- Failure to thrive in early childhood
- Anemia
- Jaundice, usually slight, gallstones
- Hepatosplenomegaly, hypersplenism
- Abnormal facies: prominence of malar eminence, frontal bossing, depression of bridge of the nose, exposure of upper central teeth
- Skull radiographs showing hair-on-end appearance due to widening of diploid spaces
- Fractures due to marrow expansion and abnormal bone structure
- Osteoporosis
- Growth retardation, primary amenorrhea, delayed puberty in males
- Leg ulcers
- Skin bronzing
- If untreated, 80% of patients die in the first decade of life
Complications

Develop as a result of:
- Chronic anemia
- Chronic transfusion → hemosiderosis and hemochromatosis
- Poor compliance with chelation therapy

- Endocrine disturbances: growth retardation, pituitary failure with impaired gonadotropins, IDDM, adrenal insufficiency, hypothyroidism
- Liver failure, cirrhosis
- Cardiac failure due to iron myocardial iron overload
- Bony deformities due to extramedullary hematopoiesis
- Osteoporosis
Management

• Transfusion therapy (when Hb falls <7g/dl)
• Hypertransfusion program used to maintain a pretransfusion Hb between 10.5 – 11.0 g/dl - corrects the anemia and suppresses ineffective erythropoiesis
• Chelation therapy to maintain serum ferritin close to 1000 ng/ml
• Splenectomy to reduce the transfusion requirements
• Bone marrow transplantation
• Gene therapy in future
• Increase HbF synthesis (trials): 5-Azacytidine, hydroxyurea, cytosine arabinoside, busulfan, butyric acid analogues
Supportive therapy:

- Folic acid
- Hepatitis B vaccination
- Treatment for congestive heart failure
- Endocrine invention
- Cholecystectomy
- Genetic counseling
- Management of osteoporosis (calcitonin, biphosphonates)
Causes of death:

- Congestive heart failure
- Arrythmia
- Sepsis secondary to increased susceptibility to infection post splenectomy
- Multiple organ failure due to hemochromatosis
Extracorpuscular hemolytic anemias

• Immune hemolytic anemia
  • Warm autoimmune hemolytic anemia - responsible antibodies IgG class
  • Cold autoimmune hemolytic anemia – IgM antibodies are cold agglutinins, and cold hemagglutinin disease, cold hemagglutinin disease usually occurs during Mycoplasma pneumoniae infection

• Nonimmune hemolytic anemia
  • Microangiopathic hemolytic anemia caused by renal, cardiac, liver disease, infections.