Anemia

Definitions:

- **Hematocrit** <41% in men or <36 in women
- **Hemoglobin** <13.5 gm\dL in men or <12 gm\dL in women

MICROCYTIC ANEMIA:

1- Iron deficiency:

- **MCC**: blood loss (GI, menstrual)
- **Presentation:** depends on severity (usual presentation of anemia): fatigue, palpitations, SOB, pallor, nail changes (brittle, spoon-shaped), glossitis, pica.
- Moderate – severe anemia -> *systolic ejection murmur* ("flow" murmur)
- **Labs**: ↓ **Hgb**, ↓ **MCV**, ↓ **MCH**, ↓ **ferritin**, ↓ **iron**, ↓ **retics**, ↑ **TIBC**, ↑ **RDW**
- **Tx**: most effective is oral therapy w\ ferrous sulfate tablets

2- Anemia of chronic disease:

- Chronic inflammation -> *hepcidin* -> binds to ferroportin -> traps iron w\in macrophages + prevents gut iron absorption
- **Labs**: ↓ **Hgb**, ↓ **MCV**, ↓ **MCH**, ↓ **iron**, ↓ **retics**, ↓ **TIBC**, ↑ **ferritin**
- **Tx**: correct underlying cause. If renal ds or chemo\radio-therapy related anemia -> iron supplementation and erythropoietin

3- Sideroblastic anemia:

- Defect in iron metabolism -> iron is trapped in the mitochondria of nucleated RBCs
- **Hereditary**: defect in aminolevulinic acid synthase or vit B6 metabolism
- **Acquired**: chloramphenicol, isoniazid, alcohol, lead poisoning
- Can progress into AML
- **Labs**: ↓ **Hgb**, ↓ **MCV**, ↑ **ferritin**, ↑ **iron**, ↑ **retics**, ↓ **TIBC**
- **Specific Dx**: Prussian Blue stain of RBCs in BM -> ringed sideroblasts + *basophilic stippling*
- **Tx**: best first step: pyridoxine -> response indicates underlying cacuse. Transfusion. BMT.

4- Thalessemia:

Alpha thalessemia:

- 1 genes deleted -> normal pt
- 2 genes deleted -> silent carrier or mild anemia (Hct 30-40%), very low MCV.
- 3 genes deleted -> *Hemoglobin H*: profound anemia (Hct 20-30%), very very low MCV
- 4 genes deleted -> *Hemoglobin Barts*: death in utero (hydrops fetalis)

Beta thalassemia:

- Trait -> mild anemia + markedly low MCV
- Major (Cooley anemia) -> *sx start after the age of 6 mo* (switch from fetal Hgb to adult Hgb) -> growth failure, hepatosplenomegaly, jaundice, bony deformities (extramedullary hematopoiesis) -> chronic anemia + transfusion dependence -> hemochromatosis, cirrhosis, CHF

- **Labs**: ↓ **Hgb**, ↓↓ **MCV** *(disproportionate to the anemia)*, **N ferritin**, **N iron**, **N TIBC**, **N RDW**
- **Specific Dx:** Hemoglobin electrophoresis.
  - **Beta thalassemia**: high levels of Hgb F and A2
  - **Alpha thalassemia**: normal levels of Hgb F and A2, if 3 genes deleted -> Hgb H
- **Blood smear** -> *target cells*, poiklocytes
- **Tx**:
  - Trait -> no Tx
  - Beta thalassemia major -> transfusion once\twice a mo
  - Chronic transfusion -> iron overload -> oral deferasirox (or deferoxamine via subQ pump)
  - Splenectomy reduces transfusion requirement (indicated in hypersplenism)
  - BMT
  - Iron supplementations is contraindicated

Hemoglobin type	Name	Component
Adult	A	α2 β2
	A2	α2 δ2
Fetal	F	α2 γ2
Abnormal	H	β4
	Bart's	γ4

MACROCYTIC ANEMIA:

1- Vitamin B12 (Cyanocobalamine) deficiency:

- **MCC**: pernicious anemia -> autoimmune destruction of parietal cells -> ↓production of intrinsic factor
- **Sx**: peripheral neuropathy, position\vibration\autonomic\motor\cranial nerves abnormalities, psychiatric, bowel\bladder\sexual dysfunx, glossitis, diarrhea, abd pain
- **Labs**: ↓ **Hgb**, ↑ **MCV**, ↓ **retics**, ↓ **B12**
- **Smear**: hypersegmented neutrophils, RBCs are oval macrocytes (while in hemolysis, liver ds, myelodysplasia give round macrocytes)
- **Specific Dx**: antibodies to IF
- **Tx**: replacement w\ vit B12 -> oral daily or parenteral (IM or subQ) monthly (recommended for neuropathy pts)
  - Early in Tx, pts might experience **hypokalemia** and fluid overload due to ↑ erythropoiesis, cellular uptake of K, and ↑ blood volume

2- Folic acid deficiency:

- **Causes**: ↓ dietary intake, pregnancy, skin losses in eczema, ↑ loss from dialysis, phenytoin, alcohol
- Same labs and presentation as vit B12 def, except ↓ **folic acid**
- **Tx**: oral replacement

HEMOLYTIC ANEMIA:

- Can happen in:
  1) Spleen\liver -> *extravascular*
  2) Vasculature itself -> *intravascular* -> hemoglobinuria
- General Sx: splenomegaly, jaundice, icterus, pruritus, gallstones, hemosiderinuria
- General Labs: normocytic anemia, ↑ LDH, ↓ haptoglobin "*hemoglobin eats haptoglobin*", ↑ total bilirubin (indirect specifically), ↑ retics (unlike anemia of chronic ds)
- *All hemolytic anemia pt should get folate supplementation!*

A. Coomb's (-) = Hereditary = Not immune-related:

- Sickle cell disease (AR)
- Hereditary spherocytosis (AD)
- Paroxysmal nocturnal hemoglobinuria (PNH) (NOT HEREDITARY!)
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency (XLR)

B. Coomb's (+) = Acquired = immune related -> sudden, associated w\ constitutional sx:

- Warm autoimmune hemolytic anemia
- Cold-agglutinin hemolytic anemia
- Drug-induced hemolytic anemia

1- Sickle cell disease:

Pathogenesis:

- Autosomal *recessive*, homozygous: normal Hb A -> *mutant Hb S*
- Point mutation: 6th position of B-chain: valine -> glutamic acid
- Hypoxia, acidosis, temp changes, dehydration, infec -> Hb molecules polymerize -> RBCs sickle -> obstruct vessels -> ischemia

Sickle cell trait:

- Heterozygous, identified by screening (clinically asx) -> genetic counselling
- Not anemic, normal life expectancy
- Associated w\ *Isosthenuria* (inability to conc urine)

Clinical features:

1. Hemolytic anemia:
   - Jaundice, pallor
   - Pigmented gallstones
   - Leads to high-output CHF
   - Aplastic crisis: provoked by virus (human parvovirus B19) -> treated by blood transfusion (recovers in 7-10 days)

(top to bottom)

CNS: stroke
Eyes: proliferative retinopathy, retinal infarcts
Lungs: infections, ACS
Heart: anemia -> high-output CHF
Blood: chronic hemolytic anemia, aplastic crisis
Kidneys: hematuria, papillary necrosis, renal failure
GI: gallstones, splenic infarctions, abdominal crises
Genitalia: priapism
Bones: painful crises, osteomyelitis, avascular necrosis

2. Vaso-occlusion:
    - Painful crisis involving bone, multiple sites, self-limiting (2-7 d)

➢ **Hand-foot syndrome (dactylitis):**
- Avascular necrosis of metacarpal\metatarsal bones -> painful swelling of dorsa of hands + feet -> in infants\early child (4-6 mo)
- Often first manifestation of SCD

➢ **Acute chest syndrome:**
- Due to repeated episodes of pulmn infarctions
- Same presentation as pneumonia: chest pain, resp distress, pulmn infiltrates, hypoxia

➢ **Splenic infarctions** (repeated episodes) -> autosplenectomy (large spleen in childhood -> not palpable by 4 yo; reduced to a small calcified ruminant)

➢ **Avascular necrosis of joints:** MC hip and shoulder

➢ **Priapism:**
- Erection lasting for 30m-3hr due to vaso-occlusion, if lasting > 3hrs -> medical emergency
- After passing urine, light exercise, cold shower -> usually subsides spont
- Prevention: hydralazine or nifedipine or using antiandrogen

➢ **Delayed growth and sexual maturation;** esp boys

➢ **CVA:** due to cerebral thrombosis, mainly in children

➢ **Eye complications:** retinal infarcts, vitreous hemorrhage, proliferative retinopathy, retinal detachment

➢ **Renal papillary necrosis + painless hematuria:** common, may cease spont

➢ **Chronic leg ulcers:** due to vaso-oculsion, typically: over lateral malleoli

➢ **Infections:**
- Functional asplenia -> more susceptible to infections (esp encapsulated bacteria: Hemophilus influenza and Strept pneumoniae)
- Splenic malfunction -> predisposition to Salmonella osteomyelitis

Diagnosis:

- **Labs**: ↓ Hgb, ↑ retics (bc of chronic compensated hemolysis), ↑ LDH, ↑ bilirubin
- **Initial test:** peripheral smear: Sickle-shaped RBCs (negative in sickle cell trait) + Howell-Jolly bodies (precipitated remnants of nuclear material in RBCs of asplenic pts)
- **Most accurate:** Hb electrophoresis
- *The first clue to parvovirus is a sudden drop in reticulocyte level*

Treatment:

- Pt education: avoid high altitudes, maintain fluid intake, treat infections promptly
- Vaccination (S. pneumoniae, H. influenza, Neisseria meningitides)
- Prophylactic penicillin for children (4 mo – 18 yr)
- Folic acid supplement (bc of chronic hemolysis)
    - Painful crises: hydration, morphine, keep pt warm, supplemental oxygen
    - **Hydroxyurea:** enhances Hb F levels -> interferes w\ sickling, reduces incidence of painful crises, accelerates healing of leg ulcers
    - Blood transfusion: based on clinical condition and not Hb levels
    - **Exchange transfusion indications** -> ACS, stroke, priapism, visual disturbance from retinal infarction. If exchange transfusion is not available -> give PRBCs

2- Hereditary spherocytosis:

- Autosomal *dominant* -> loss of *spectrin* in RBC membrane
- **Sx**: mile\moderate sx of anemia, splenomegaly, jaundice
- **Labs**: ↓ Hgb, -\↑MCV, **↑ MCHC**, ↑retics, ↑ LDH, ↑ bilirubin
- **Blood smear** -> spherocytes :)
- **Negative Coomb's test**
- **+ Osmotic fragility test** -> cells have an ↑ sensitivity to lysis in hypotonic solution
- **Tx**: folate + elective splenectomy

3- Paroxysmal nocturnal hemoglobinuria (PNH):

- Idiopathic\not hereditary -> clonal defect of **GPI** in RBC membrane -> ↑ *complementation* -> intravascular hemolysis
- *Why occurs at night?* Complementation is encouraged by the slightly acidotic state during sleep
- **Sx**: anemia sx, dark\cola\tea-colored urine when pt wakes up -> normalizes as the day goes on, increased risk of *venous thrombosis* (hepatic "***Budd-Chiari***", dermal "painful skin nodules)
- **Dx**: acidified serum lysis "Ham" test, flow cytometry for CD55\CD59
- **Tx**: iron + folate, steroids if severe, elective anticoagulation (mandatory if pregnant or thombo-embolic events have occured)

4- G6PD:

- **X-linked recessive** (more in boys) -> deficiency in G6PD -> reduction of NADPH (antioxidant)
- **Sx**: children + acute -> linked to infection, drugs (sulfas, nitrofurantoin), foods (fava beans)
- **Blood smear** -> *Heinz bodies* + *Bite cells*
- **Tx**: stop offending agent + hydration

5- Autoimmune\warm hemolytic anemia:

- **Causes**: idiopathic, lymphoproliferative ds (CLL, lymphoma), autoimmune ds (SLE, RA, scleroderma)
- **Initial test** -> Positive Coomb's test = direct antiglobulin test (DAT)
- Negative cold-agglutinin titer
- **Tx**: folate + steroids, transfusion if necessary

6- Cold-agglutinin hemolytic anemia:

- **Causes**: usually linked to an infection -> ***Mycoplasmia***, EBV, HIV
- **Key differentiator**: worsend w\ exposure to cold -> purplish discoloration of fingers\toes
- **Initial test** -> Positive Coomb's test = direct antiglobulin test (DAT)
- Positive cold-agglutinin titer
- **Tx**: folate + avoid cold conditions, Rituximab if necessary

7- Drug-induced hemolytic anemia:

- **MCC**: ***cephalosporin*** abx, levofloxacin, nitrofurantoin, rifampin, methyldopa
- **Initial test** -> Positive Coomb's test = direct antiglobulin test (DAT)
- **Tx**: stop the drug + folate

APLASTIC ANEMIA:

- Bone marrow failure -> pancytopenia (anemia, leukopenia, thrombocytopenia)
- **Causes**:
  - Radiation
  - Toxins: benzene
  - Drugs: NSAIDs, chloramphenicol
  - Alcohol
  - Chemo: alkylating agents
  - Infections: hepatitis, HIV, CMV, EBV, parvovirus B19
- **Sx**: bleeding (thrombocytopenia), fatigue (anemia), infections (neutropenia)
- **Dx**: pancytopenia, BM biopsy (*confirmatory*)
- **Tx**: BMT (if young and healthy), immunosuppressive agents (anti-thymocyte globulin, cyclosporine, prednisone)

Random notes:

- **Ferritin** and **hepcidin** are acute phase reactants -> elevated in any pt w\ inflammation
- TIBC = transferrin
- Hereditary spherocytosis, PNh, G6PD -> are at an increased risk of aplastic anemia (esp w\ parvovirus B19)

Anemia	Hgb	MCV	RDW	Retics	Ferritin	Iron	TIBC
Iron deficiency	↓	↓	↑	↓	↓	↓	↑
Anemia of chronic disease	↓	↓	↑	↓	↑	↓	↓
Sideroblastic	↓	↓	↑	↑	↑	↑	↓
Thalessemia	↓	↓↓	N		N	N	N

References:

- *Kaplan step 2 lecture notes*
- *Paul Bolin's videos*
- *Step up to medicine*