HEMATOLOGY BASICS

- **RBCs**: deliver oxygen to tissues
  - 2 components: heme and globulin
    - **Heme**: iron:Fe that binds and releases O2
    - **Globulin**: unit comprised of 2 alpha chains and 2 beta chains

- **Iron (Fe) Regulation**
  - **Iron deficiency**: anemia, decreased ability to deliver O2 to tissues
  - **Iron overload**: cellular toxicity caused by excess free radical production
  - **Transferrin & TIBC**:
    - *Transferrin*: binds and transports Fe throughout body; decreases Fe toxicity
    - *TIBC*: binding capacity of transferrin to Fe; indirectly measures transferrin levels
    - Inc. transferrin + increased TIBC = Fe deficiency
    - Dec. transferrin + decreased TIBC = anemia of chronic dz
  - **Ferritin**: stores Fe
    - Dec. ferritin = Fe deficiency anemia (stores depleted)
    - Inc. ferritin = anemia of chronic disease
      - Hepatic response during inflammation produces acute phase reactants that sequester Fe making it unavailable to bacteria; ferritin releases along with other mediators
      - Inc. haptoglobin binds free hemoglobin
      - Inc. CRP increases opsonization (marking cell for destruction)
      - Inc. hepcidin prevents iron release from macrophages
  - **Serum Fe**: measures amount of Fe bound to transferrin
    - Decreased serum Fe = Fe deficiency anemia or anemia of chronic dz
      - Distinguish with TIBC and ferritin levels
        - *Fe deficiency anemia* – inc. serum Fe, dec. ferritin, inc. TIBC
        - *Anemia of chronic dz* – dec. serum Fe, inc. ferritin, dec. TIBC
      - Inc. serum Fe = Fe overload states (hemochromatosis)

- **RBC maturation**
  - Mature in bone marrow, loose nucleus throughout maturation
  - **Reticulocytes**: immature RBC’s released from bone marrow into circulation; still have RNA which makes them larger than fully matured RBCs
    - **Reticulocytosis**: increased reticulocyte production
      - Demonstrates appropriate bone marrow response to blood loss or hemolytic anemia
    - **Dec. reticulocytes**: decreased RBC production
      - Bone marrow not able to replenish RBC’s (Fe, B12, folate deficiencies, ACD)

- **RBC lifecycle**
  - Lifespan = 120 days
  - Old RBCs broken down by macrophages in spleen (and liver)
  - Heme broken down to biliverdin (green pigment) → unconjugated (indirect) bilirubin (yellow pigment)
  - Unconjugated bilirubin conjugated with glucaronic acid in liver by UGT enzyme (now water-soluble and makes up bile)
    - **Jaundice**: yellowing of skin/sclera (more commonly d/t build up of indirect bili)
  - **Indirect hyperbili**: disorders with increased destruction of RBCs exceeds liver capacity to conjugate bili (ex: hemolytic anemia)
  - **Direct hyperbili**: associated with dark urine, can also be seen with hemolytic anemia
### Hematologic and Oncologic

#### Anemias

- **Low Hgb, Hct, & RBC**
  - Factors affecting Hgb (plasma:blood volume), hydration, pregnancy, environment, age, gender

- **Symptoms**
  - Dyspnea, DOE, fatigue, weakness, dizziness, palpitations, bounding pulses, roaring pulses in ears, pallor, tachycardia, hypotension, pica (in Fe-def)
  - Look for jaundice, murmurs, splenomegaly, AMS

- **Microcytic (MCV <80):**
  - Iron deficiency, thalassemia, chronic blood loss (GI bleed, menometrorrhagia), chronic dz/inflammation (late), lead poisoning, sideroblastic (EtOH abuse)

- **Normocytic (80-100):**
  - Acute blood loss, chronic dz (infx, inflammation, malignancy), bone marrow suppression, aplastic anemia, chronic renal insufficiency, hypothyroidism, iron def (early)

- **Macrocytic (MCV >100):**
  - B12 def, folate def, EtOH abuse (target cells), liver disease, reticulocytosis / hemolytic anemia, AML, drug-induced, hypothyroidism (less common)

- **Reticulocyte Index indicates if bone marrow is responding appropriately to anemia**

- **Etiologies:** blood loss, increased RBC destruction, decreased RBC production (can be a mixed picture)

#### Clinical manifestations

- **General:** weakness, fatigue
- **Eye:** retinal hemorrhages
- **Cardiovascular:** palpitations, tachycardia, high-output failure, orthostatic hypotension
- **Pulmonary:** CP, SOB, tachypnea
- **Abd:** HSM, ascites
- **Rectal:** (+) hemoccult blood
- **Skin:** pallor (decreased color of palmar creases, pale conjunctiva), purpura, petechiae, jaundice
- **Neurologic:** dizziness, syncope, headache, neuropathies, AMS, vertigo

#### Work up

- CBC with indices, peripheral blood smear, bone marrow (gold standard, rarely done)

#### Reticulocyte count

- Shows body’s response
- **Inc. reticulocytes** = bone marrow response to hemolysis or blood loss
- **Dec. reticulocytes** = no response from bone marrow, deficient production of RBC’s

#### Morphologic approach of reticulocytosis

- **Normocytic anemia:** 80-100
- **Microcytic anemia:** MCV <80
- **Macrocytic anemia:** MCV >100

#### Anemia of chronic disease

- Infx, inflammation, malignancy → decreased RBC production vs. increased loss
- ↓ serum iron, transferrin sat, TIBC, retic count
- ↑ ferritin

- Tx: transfusion of packed RBCs, EPO

#### Etiologies

- chronic inflammatory conditions (infx, inflammation, autoimmune, malignancy)
- Decreased serum Fe to prevent availability to pathogens
- **Hepcidin:** produced by liver; inhibits macrophage Fe release
- Increased ferritin: sequesters iron in storage
- Cytokines: inhibit erythropoietin

#### Symptoms

- Asymptomatic
- Symptoms of infection
- Symptoms of disease causing ACD

#### Diagnosis

- Increased ferritin
- Decreased TIBC
- Decreased serum Fe
- Mild normochromic normocytic anemia → (May be microcytic, hypochromic in early phase)
- Hgb usually <9-10

#### Treatment

- Tx underlying disease
- Erythropoietin-A if renal disease

### Iron deficiency anemia

- Fe deficiency, poor diet, chronic blood loss (GI bleed, menometrorrhagia), malabsorption, increased requirements (pregnancy)
- Causes of ½ cases of anemia
- Caused by dec. RBC production d/t deficiency of Fe

#### Symptoms

- Anemia sx’s
- Pagophagia (ice craving)
- Pica
- Angular cheilitis
- Koilonychia (nail spooning)
- **Plummer Vinson Syndrome:** dysphagia + esophageal webs + atrophic glossitis + Fe deficiency

#### Diagnosis

- ↓ serum iron, ferritin, transferrin sat (serum Fe/TIBC), MCV, MCH, retic count
- ↑ TIBC, platelet count (slightly)

#### Treatment

- Iron replacement therapy with ferrous sulfate (PO preferred, IV available)
- Consider GI s/e with iron replacement → start low and then titrate up
### Lymphocytic Leukemia

**Acute Lymphocytic Leukemia (ALL)**
- Malignancy of lymphoid stem cells in BM
- B cell, T cell, null type (non-B/T cell), Affects LN, spleen, liver
- MC childhood malignancy (peak age 3-7yo)
- Increased incidence in children >5yo w/Down’s syndrome

**Symptoms**
- Fatigue, lethargy, bone pain
- CNS sx: HA, stiff neck, visual changes, vomiting
- Pallor, petechiae, bruising

**Diagnosis**
- Bone marrow: hypercellular >20% blasts, *(Acute blastic crisis = acute leukemia), WBC 5-100K, Decreased platelets, Anemia*

**Treatment**
- Oral chemotherapy *(hydroxyurea, imatinib)*
- Responsive to combination chemo (remission >90%)
- Stem cell transplant if relapse
- MTX for CNS disease

**Chronic Lymphocytic Leukemia (CLL)**
- B cell clonal malignancy, MC form of leukemia in adults >50yo
- Possible etiologies: viral infx, EBV, HIV

**Symptoms**
- Asx (often found incidentally on blood tests)
- Fatigue, DOE, increased infection
- HSM, LAD (lymphocytes accumulate in organs)

**Diagnosis**
- Peripheral smear: well-differentiated lymphocytes w/scattered smudge cells
- *(Smudge cell: fragile B cells that smudge on slide)*

**Treatment**
- Observation if indolent
- Acute blastic crisis: combination chemo
- Chronic dz: PO chemo

### Myelogenous Leukemia

**Acute Myelogenous leukemia (AML)**
- Malignancy of myeloid stem cells, MC >50yo
- MC acute leukemia in adults (80% of cases)

**Symptoms**
- Anemia, thrombocytopenia, neutropenia, Gingival hyperplasia, bone pain, leukostasis *(WBC >100K)*
- CNS deficits: HA, confusion, TIA
- Pulmonary: resp. distress, dyspnea

**Diagnosis**
- Peripheral smear: auer rods
- (Auer rods: rods of cytoplasmic granules)
- (Blastic crisis undifferentiated on peripheral smear)
- Bone marrow: >20% blasts
- *(Acute blastic crisis = acute leukemia)*

**Treatment**
- Combination chemo, bone marrow transplant

**Chronic Myelogenous Leukemia (CML)**
- Malignancy of myeloid stem cells, MC >50yo
- Philadelphia chrm: translocation @ chrm 9 and 22 → BCR-ABL
- Mutation causes dysregulated tyrosine kinase activity

**Symptoms**
- 70% asx, become symptomatic after developing blastic crisis (acute leukemia)

**Diagnosis**
- Peripheral smear: well-differentiated cells
- Acute: <5% blasts
- Accelerated: 5-30% blasts
- Acute blastic crisis: >20% blasts
- Marked increased WBC (<100K), increased LDH
- Decreased leukocyte alkaline phosphatase score
- Philadelphia chrm

**Tx**
- Philadelphia chrm (+): PO chemotherapy *(Imatinib, hydroxyurea) Imatinib → inhibits tyrosine kinase activity*

### Thrombotic Thrombocytopenic Purpura (TTP)

- Decrease in ADAMTS13 *(vWF cleaving protease) → clotting*
- Large vWF multimers adhere to plt causing endothelium platelet adhesion → small vessel thrombosis → hemolytic anemia
- Primary: idiopathic (autoimmune) → anti-ab leads to dec. ADAMTS13
- Secondary: malignancy, bone marrow transplant, estrogen, pregnancy, HIV *(HIV doubled incidence of TTP)*

**Symptoms**
- Pentad:
  - Thrombocytopenia: petechiae, purpura, mucocutaneous bleeding
  - Microangiopathic hemolytic anemia: anemia, jaundice, schistocytes
  - RF/uremia: not as common
  - Neurologic sx’s: HA, CVA, AMS
  - Fever: rare

**Diagnosis**
- Thrombocytopenia, normal coags (PT/PTT)
- Problem is decreased platelets not clotting factors → normal coags → differentiate from DIC
- Hemolytic anemia
- Peripheral smear: increased retics and schistocytes
- Increased LDH & bilirubin, decreased haptoglobin, Coomb’s neg

**Treatment**
- Plasmapheresis = Tx of choice, removes anti-ab to ADAMTS13 & adds missing ADAMTS13 to serum
- Monitor LDH/plts until normal X2 days
- Immunosuppression → *Steroids*, cyclophosphamides
- No platelet transfusions *(may cause thrombosis)*
- Splenectomy *(if refractory to tx)*
Idiopathic (Autoimmune) Thrombocytopenic Purpura (ITP)

- Acquired, abnormal isolated thrombocytopenia
- Primary: idiopathic
- Secondary: immune-mediated (assoc. w/underlying disease – SLE, HIV, HCV)
- Immune-mediated: anti-α to platelets with splenic platelet destruction
  - Often follows acute viral infx that → anti-ab vs. GPIIb/IIIa receptor on pts
- Acute ITP: MC in children (boys) post-viral infx (self-limiting)
- Chronic ITP: adults, often recurrent

Symptoms
- Often asymptomatic, increased mucocutaneous bleeding (purpua, bruises, petechiae, bullae, epistaxis, menorrhagia, bleeding of gums)

Diagnosis
- Isolated thrombocytopenia w/normal coags (Normal coags b/c plt disorder not due to coags!!)
  - Peripheral smear may show megakaryocytes or large platelets

Treatment
- Children → Observation (80% resolve w/in 6mo), +/- IVIG
- Adults → Corticosteroids, IVIG, splenectomy if refractory, platelet transfusion only if <20K to prevent spontaneous ICH

Clotting disorders

Hemophilia A (Factor VIII Def)

- Lack of factor VIII affects intrinsic pathway → failure to form hematoma
- MC type of hemophilia (80%), X-linked recessive trait (occurs almost only in males), can be caused by spontaneous mutation
- 1st episode usually occurs <18 yo

Symptoms
- Hemarthrosis (80%) → +/- bleed in weight bearing joints (ankles, knees, elbows)
- Excessive hemorrhage in response to trauma/surgery → Bleeding w/tooth extraction
- Epistaxis, bruising, hematuria/blood in stool, less commonly present with petechial/purpua (plt fxn normal)
- Spontaneous hemorrhage only seen w/severe forms

Diagnosis
- Low factor VIII, Prolonged PTT, Normal PT/bleeding time/fibrinogen levels/plt levels
  - Mixing study w/normal plasma will correct PTT

Treatment
- Factor VII infusion to levels 25-100%, Desmopression (DDAVP) (transiently inc. VIII & vWF; can be used pre-procedures)

Hemophilia B (Christmas Dz, Factor IX Def)

- X-linked recessive trait (occurs almost only in males)

Symptoms
- Clinically indistinguishable from Hemophilia A, Deep tissue bleeding

Diagnosis
- Decreased serum factor IX, Prolonged PTT (corrects w/mixing study)

Treatment
- Factor IX infusion, Desmopression NOT helpful (only used in Hemo A & vWD)

Von Willebrand Dz

- Deficient vWF necessary for plt adhesion & VIII degradation
- Autosomal dominant, MC hereditary bleeding disorder, consider if bleeding w/minor cuts

Symptoms
- Mucocutaneous bleeding: easy bruising, epistaxis, gums, GI, menorrhagia (Incisional bleeding not as much as hemophilia)
- Petechiae: common in wVF (Petechiae rare in hemophiliacs)

Diagnosis
- Decreased vWF levels, prolonged PTT (PTT corrects w/mixing study)
  - Bleeding time and prolonged PTT worse w/aspirin
  - Decreased ristocetin activity test (GOLD STANDARD; ristocetin = abx that causes plt aggregation in vitro)

Treatment
- Type 1: 75% quant. dz
  - Mild dz: no tx needed
  - Moderate: desmopressin (inc. vWF & VIII)
  - Severe: cryoprecipitate
- Type 2: qualitative deficiency → Desmopressin
- Type III: severely absence of vWF (rare) → vWF + VIII, avoid ASA
### Hodgkin's Lymphoma
- Lymphocyte neoplasm, Associated w/EBV
- Bimodal → peaks 20yo & 50yo, MC in boys
- Contiguous orderly spread to LN
- MC affects upper body LN → neck, axilla, shoulder, abd

#### Symptoms
- Painless LAD (may be induced by EtOH)
- HSM, anemia, pruritis
- Systemic B symptoms: pel-ebstein fevers (cyclic fevers over 1-2wks), night sweats, weight loss

#### Diagnosis
- Excisional bx: Reed Sternberg cell pathognomonic
- Only associated with HL
- Associated with clonal B cell proliferation
- Large cells with bilobed or multilobular nucleus
- Mediastinal LAD
- PET/CT for staging

#### Treatment
- Radiation therapy
- Chemotherapy
- HL highly curable compared to NHL

### Non-Hodgkin's Lymphoma
- Lymphocyte neoplasm
- Multiple variation → Diffuse B cell, T cell, follicular, Burkitt
- Follicular: MC indolent form
- DLBCL: MC aggressive form
- MC >50yo, MC affects peripheral LN
- Risk factors → Age, immunosuppression (HIV, viral infx), connective tissue dz, FHx, XRT

#### Symptoms
- Local → painless LAD, splenomegaly
- Extra-nodal → Gl, skin, skin MC sites, testicular enlargement, mediastinal masses, abd pain (Burkitt)
- Systemic B symptoms less common in NHL (+/- seen in advanced disease)

#### Diagnosis
- PT/CT scan for staging

#### Treatment
- Follicular → Generally not curable, can be maintained on rituximab (ab vs. CD20)
- Diffuse Large B Cell → Curable with chemo, R-CHOP

### Aplastic anemia
- Diminished/absent hematopoietic stem cells in bone marrow
- MC due to destruction of pluriotent stem cells
- Consider in pts presenting with pancytopenia

#### Etiologies:
- Cytotoxic drugs: chemotherapy
- Drugs: anticonvulsants, antibiotics (sulfonamides, chloramphenicol), NSAIDs (indomethacin), anti-thyroid medds, gold, arenesscials
- Toxic chemicals: benzene, solvents, glue vapors
- Viral infx: EBV, seronegative hepatitis, HIV, HSV
- Immune disorders: eosinophilic fasciitis, SLE, graft
- Misc.: paroxysmal nocturnal hemoglobinuria, thymoma, pregnancy, anorexia nervosa

#### Symptoms
- Fatigue, cardiopulmonary compromise
- Recurrent infections (d/t profound neutropenia)
- Mucosal bleeding, increased menstrual flow (d/t thrombocytopenia), petechiae

#### Diagnosis
- Peripheral smear:
  - Normocytic/macrocytic RBCs
  - Marked reduction in reticulocytes
  - Decreased neutrophils and plts
  - No abnormal WBCs not present
- Bone marrow bx:
  - Profoundly hypocellular w/disease in all elements
  - Marrow space mainly composed of fat cells and marrow stroma
  - Residual hematopoietic cells normal
  - No infiltration of malignant cells or fibrosis

#### Treatment
- Tx underlying cause, blood transfusions
- Bone marrow transplants (if in good health status)
- Immunosuppression medications (anti-thymocyte globulin (ATG), cyclosporine) → used for acquired aplastic anemia
- Medications that stimulate bone marrow (G-CSF, cytokines, GM-CSF)

### Multiple Myeloma
- Proliferation of single clone of plasma cells → increased monoclonal ab (IgG, IgA)
- Plasma cells accumulate in BM interrupting marrow’s normal production
- Risk factors → >65yo, AA’s, Men, HSV exposure

#### Symptoms (CRAB)
- Hypercalcemia (hyporeflexia)
  - Only hematologic malignancy assoc. w/elevated calcium
- Renal failure
  - Protein kidney ab light-chain deposition
  - +/- neurologic involvement
- Anemia: fatigue, pallor, weakness, weight loss, HSM, soft tissue masses
- Bone pain
  - MC spine and ribs, osteolytic lesions & fx
  - Skeletal destruction, spinal cord compression (plasma cells form tumor), radiculopathy
- Recurrent infx
  - Strep pneumonia
  - Gram (-)’s
  - D/t leukopenia

#### Diagnosis
- Serum protein electrophoresis (SPEP)
  - Monoclonal protein spike
- IgG 60%, IgA 20%
- Urine protein electrophoresis (UPEP)
  - Bence-Jones proteins → kappa/lambda light chains
- CBC → Rouleaux formations (RBC’s stick together d/t inc. plasma protein) → inc. ESR
- Skull XR → Punched out lesions
- Marrow bx → Plasmacytosis
- Bone scans not helpful

#### Treatment
- Stem cell transplant
- Neo-adjuvant therapy: thalidomide
- Bisphosphonates (to help with bony manifestations)
Sickle Cell Disease

- **Sickle Cell** → **sickled cells** on peripheral smear → Autosomal recessive genetic disorder of HgbSS
- **Sickle cell trait**: 8% AA’s, heterozygous, usually asx unless severe hypoxia/dehydration, may have hematuria; malaria resistance
- **Early signs** → Begin @6mo when HgbSS replaces HgbF, **Dactylitis** MC 1st sx @6-9mo, delayed G&D, fever, infection
- **Infections**:
  - Osteomyelitis (Salmonella)
  - Functional asplenia (inc. risk of infx d/t encapsulated organisms → S. pneumonia, H. flu, N. meningitides, GBS, klebsiella)
  - Aplastic crisis assoc. w/parvovirus B-19 & folate def.
- **Hemolytic anemia** → jaundice, gallstones, pneumo meningitis common
- **Microthrombosis** → skeletal, skin ulcers, stroke, painful occlusive crisis (cold weather, ETOH, pregnancy, **acute chest syndrome**)
  - Splenic sequestration crisis: vaso-occlusion = acute SM & dec. Hgb (can be fatal); leads to fxn asplenia in adulthood
  - Dec. O2 affinity of HgbS: pulmonary HTN, CHF, fatigue, SOB, renal medullary infarctions → inability to conc. Urine
- **Diagnosis**
  - Hgb electrophoresis
  - **Peripheral smear**: target cells, sickled erythrocytes +/- Howell-Jolly bodies (indicates fxn asplenia)
  - Sickledex test detects abnormal Hbs → will detect both carrier & disease, but does not differentiate between the two (AS vs. SS) → need to do hemoglobin gel electrophoresis to determine if heterozygote or homozygote
- **Treatment**
  - **Pain control** → IV fluids + O2
  - Meperidine (Demerol) contraindicated in SCD pts (may lead to seizures and renal failure)
  - **Hydroxyurea** → for severe pain crisis
  - Folic acid supplementation
  - Immunize children for S. pneumonia, H. flu type B, N. meningococcus (SHIN)
  - RBC transfusions
  - Plasma exchange indicated for children w/CVA symptoms
  - Allogenic stem cell transplant → Only possible curative management, associated w/significant S/E’s

Hemolytic anemia (G6PD deficiency, Sickle cell, Thalessemia)

- **Clues** → **brown urine**, splenomegaly, jaundice, scleral icterus
- Increased retic count, indirect (bilir), urinary bilirubin, LDH
- **Autoimmune Hemolytic Anemias** (AHAs) = warm vs. cold autoabs (Direct Coombs Test)

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

- X-linked recessive trait, primarily affects AA males
- Deficiency of RBC protective enzyme against oxidative stress
- **Oxidative stress oxidizes Hgb into methemoglobin**
  - Increases RBC membrane damage
  - Hgb fragile → denatures (Heinz bodies)
  - Splenic macrophages destroy damaged RBCs leading to **episodic hemolytic anemia**
- **Oxidative stresses causes**: Infection (MC), fava beans
  - Meds (Sulfa drugs – Bactrim, antimalarials, NSAIDs)
  - Methylene blue, INH, **fluoroquinolones**, ASA)

- **Symptoms**
  - Asx until exposure, sx occur 2-4 days post exposure
  - **Episodic non-immune acute hemolytic anemia**:
    - Back/abd pain, symptoms of anemia
    - Jaundice, dark urine, splenomegaly
    - Hemolytic crisis (splenic RBC sequestration)
    - Neonatal jaundice/acute renal failure

- **Diagnosis**
  - **Peripheral smear**: hemolytic anemia (during acute phase, smear normal if not in acute stage)
    - Schistocytes (bite/fragmented cells)
    - +/- Heinz bodies
  - Labs: inc. reticulocytes, inc. indirect bili
  - Enzyme assays: fluorescent spot test

- **Treatment**
  - Usually self-limited, avoid offending foods and drugs
  - **Severe anemia** → Fe/folic acid supplementation, +/- blood transfusions

Polycythemia Vera

- Myeloproliferation disease, presence of elevated RBC mass
- 50-70 yo
- Independent of EPO stimulation vs physiologically appropriate (hypoxia)
- Secondary: physiologically inappropriate (EPO due renal cysts/tumors, high altitude)
- **Symptoms** → Asymptomatic, headache, dizzy, weak, sweaty, pruritis
  - Erythromelalgia → burning pain with erythema, pallor or cyanosis in the presence of palpable pulses noted in the hands and feet

- **Physical Exam**
  - Splenomegaly, hepatomegaly, facial plethora-red face, conjunctival injection

- **Diagnosis**
  - Elevated RBC mass! Increased hgb ->18.5
  - Thrombocytosis >450,000, leukocytosis >10,500, EPO low
  - **JAK2 mutation positive** (seen in 96% of patients)
    - The JAK2 gene is located on the short (p) arm of what chromosome 9 at position 24
  - Uric acid levels will be high (uric acid levels are always high when cells are being destroyed as in hemolysis, chemotherapy or radiation therapy)

- **Treatment**
  - phlebotomy- maintain HCT <45% → the goal of blood letting is to reduce the thickness of the blood and prevent bleeding and clotting problems
  - 40-60% of patients untreated with Polycythemia Vera will develop a blood clot
  - Low iron diet
  - Hydroxyurea- myelosuppressive agent
  - Myleran (busulfan)
**Hemolytic Anemia Overview**

- **Caused by increased RBC destruction in which rate of destruction > bone marrow’s capacity to replace RBC’s**
- **Intrinsic:** inherited (sickle cell, thalassemia, G6PD deficiency, hereditary spherocytosis)
- **Extrinsic:** acquired (autoimmune hemolytic anemia, DIC, TTP, HUS, paroxysmal nocturnal hemoglobinuria, hypersplenism)

**Characteristics**

- Reticulocytosis
- Increased serum LDH
- Increased indirect bilirubin (jaundice, dark urine indicates increased direct bili)
- Decreased haptoglobin
- Schistocytes on peripheral smear (hemolysis of damaged cells → sheared RBC’s in spleen)

**Distinguishing Factors**

- **Sickle Cell Anemia:** sickled cells on peripheral smear, Hgb S on Hgb electrophoresis
- **Thalassemia:** normal/inc. serum Fe, no response to Fe tx
  - **Alpha thalassemia**: normal ratios of HgbA, HgbA2, HgbF on electrophoresis
  - **Beta thalassemia**: decreased HgbA, increased HgbA2, increased HgbF on electrophoresis
- **G6PD deficiency:** episodic hemolytic anemia (triggered by sulfa drugs, fava beans, infections)
- **Hereditary spherocytosis:** microspherocytes, Coombs (-), (+) osmotic fragility test
- **Autoimmune hemolytic anemia:** microspherocytes, Coombs (+)
- **TTP & HUS:** normal coags, clinical differentiation between TTP & HUS
  - **TTP triad:** thrombocytopenia, hemolytic anemia, kidney damage, neuro sx, fevers
  - **HUS triad:** thrombocytopenia, hemolytic anemia, kidney damage
- **DIC:** abnormal coags (prolonged PT & PTT)
- **Paroxysmal nocturnal hemoglobinuria:** dark urine worse in AM

**Alpha Thalassemia**

- Decreased alpha-globin chain production
- Eventually leads to **excess beta chains**
- MC in SE Asians (68%), Africans (30%), Mediterranean (5-10%)

**Symptoms:** 4 genes involved →

- Silent carrier: 3 normal genes; clinically normal
- a-T minor: 2 normal genes; asx +/- mild anemia sx’s, increased RBC and decreased MCV
- a-T intermedia: 1 normal gene; severe anemia, pallor, HSM, microcytic hemolytic anemia, frontal skull/maxillary overgrowth, pathologic fx, pigmented gallstones, Fe overload; **Heinz bodies on PS**
- a-Thalassemia Major (hydrops fetalis): no functioning genes, still childbirth or fetal death from high output failure

**Diagnosis**

- Peripheral smear: target cells, tear drop cells, basophilic stippling, inc. RBC count
- Normal/increased Fe stores, dec. MCV (60-75)
- Hgb electrophoresis: normal Hgb ratios (distinguishes alpha from beta)

**Treatment**

- Mild disease (a-trait) → No tx needed
- Moderate dz → Folate (if reticulocytosis, prevents deficiency), **avoid oxidative stress (Sulfa drugs)**
- Severe dz → blood transfusions (weekly), Iron chelating agents (deferoxamine, deferasirox → prevent iron overload, removes excess iron w/chronic transfusions), splenectomy
  - Bone marrow transplant definitive tx (needs vit C & folate supplementation)

**Beta Thalassemia**

- Decreased production of beta globin chains
- Leads to excess **alpha chains**
- MC in Mediterranean, Africans, Indians, Asians

**Symptoms:** 2 genes involved →

- B-thalassemia trait: MC type; 1 normal gene (heterozygous); asx +/- mild anemia sx’s
- B-thalassemia intermedia: mild homozygous form; anemia, HSM, bony dz
- B-thalassemia major (Cooley’s anemia): both genes mutated; pts normal at birth (d/t fetal HgbF) and become sx @6mo, HSM, severe hemolytic anemia (jaundice, dyspnea, pallor), osteopenic fx, frontal bossing (d/t excessive a-chains unable to form tetramers)

**Diagnosis**

- Peripheral smear: target cells, tear drop cells, basophilic stippling, nucleated RBCs
- Suspect thalassemia in pts w/microcytosis & normal/increased serum Fe and increased RBC count
- Blood pic may resemble iron deficiency but normal/increased serum Fe
- Hgb electrophoresis
- XR: skull bossing (hair on end appearance)

**Treatment**

- B-thalassemia trait (minor) → typically does not require tx, genetic counseling
  - B-thalassemia major (severe) → Transfusion weekly, deferoxamine (chelating agent) to prevent iron overload/remove excess iron, bone marrow transplantation, Vit C, folate, Splenectomy

**Thalassemia** → reduced globin synthesis, m/c in Asian & Mediterranean descent, microcytic megaloblastic, **target morphology**

- Genetic benefit against malaria (distribution follows p. falciparum)
- Dec. production of globulin chains
- Most adults are heterozygotes
- Seen in pts with microcytic anemia with normal-inc. serum Fe or no response to Fe replacement
**B12/Folate deficiency - Megaloblastic/Macrocytic anemia**

- B12 & Folate are co-factors for thymine needed for DNA synthesis, abnormal synthesis of DNA and erythroid precursors
- Stores last for yrs, absorption occurs in ileum
- Malabsorption → pernicious anemia MC (associated with hypothyroidism), EtOH, Crohn’s, meds (H2RA, PPIs)
- Decreased intake (found in animal products)
- Symptoms → pallor, glossitis, stomatitis, GI sx, psych sx, Hyperhomocysteinemia, peripheral neuropathy LE, abnormal Babinski
- Dx → Peripheral smear: MCV >115, hyper-segmented neutrophils, macroovalocytosis
  - Increased serum homocysteine
  - Increased methylmalonic acid
  - Dec. B12 <170 (normal = 240)
  - Pernicious anemia: (+) intrinsic factor ab, parietal cell ab, inc. gastrin levels, (+) Schilling test
- Tx → B12 replacement (IM)
  - Watch for hypokalemia (reticulocytes produced during tx take up large amounts of K)
- Complications → Spinal cord demyelination & degeneration (ataxia, weakness, vibratory, sensory, and perception deficits, dec. DTR)

**Folate Deficiency**

- Required for DNA synthesis, absorption occurs in jejunum
- Etiologies
  - Malabsorption
  - Pregnancy
  - Hemolysis (inc. cell turnover deplete folate stores)
  - Meds (MTX, bactrim)
- Symptoms
  - Pallor, glossitis, stomatitis, GI sx, psych sx, hyperhomocysteinemia
  - No neurologic sx’s
- Diagnosis
  - Peripheral smear: MCV > 115, hyper-segmented neutrophils, ↓ retic count
  - Hypersegmented PMNs and/or megaloblasts (large immature RBCs) on smear
  - Schilling Test
  - Dec. folate
  - Normal B12
- Treatment
  - Folic acid 1mg PO qid
  - PO and aqueous folate replacement therapies
- Complications → Fetal neural tube deficits if during pregnancy

**Hemolytic Uremic Syndrome**

- Platelet activation by exotoxins
- Shigella toxin, Shiga-like toxin E. coli 0157:H7
- Toxins damage vascular endothelium → activate plts → microthrombi formation → plts depleted → thrombocytopenia & hemolytic anemia
- Toxins also damage kidney → uremia, HTN
- MC in children: EHEC 0157:H7 (5-10 days post-infx), shigella, salmonella
  - Suspect HUS if RF in children w/diarrhea prodrome
- Adults: HIV, SLE, APL
- Symptoms
  - Triad:
    - Thrombocytopenia: bruising, purpura, bleeding
    - Microangiopathic hemolytic anemia: anemia, jaundice, schistocytes
    - RF/uremia: more common in HUS than TTP
      - Lacks fever & neurologic sx’s seen in TTP
- Diagnosis
  - Labs → Thrombocytopenia, normal coags (PT/PTT)
  - Inc. BUN/Cr
  - Problem is dec. plts not clotting factors → normal coags → differentiate from DIC
- Hemolytic anemia
  - Peripheral smear: increased. retics, schistocytes
  - Increased LDH, increased bili
  - Decreased haptoglobin
  - Coomb’s neg, splenomegaly
  - Similar labs to TTP → hemolytic anemia & normal coags!
- Treatment
  - Observation in most children (usually self-limiting)
  - Plasmapharesis (+/-FFP) indications:
    - Severe
    - Neuro complications
    - Non-renal complications
  - Abx may worsen condition (d/t inc. vertoxin release in bacterial cell lysis)

**Factov V Leiden**

- Factor V Leiden is the most common inherited thrombophilia
- Major clinical manifestation
  - VTE, however, only a small percentage of individuals with FVL will develop VTE in their lifetime
- FVL may contribute to arterial thromboembolism (myocardial infarction, stroke) or pregnancy complications (early fetal loss), but the magnitude of the effect is likely to be small relative to other risk factors
- Treatment
  - For asymptomatic individuals who are heterozygous for FVL don’t treat routinely with anticoagulation, with the exception of certain high-risk situations such as surgery, pregnancy, or the presence of additional thrombophilic mutations.

**Can also be related to EtOH abuse, liver disease, hypothyroidism, and disease states that cause abnormal RBC maturation (MDS, acute leukemia, reticulocytosis)**
**Lead Poisoning**
- Children with lead poisoning typically are asymptomatic.
- Diagnosis usually is made through measurement of an elevated blood lead level (BLL) during routine blood lead screening.
- False-positive elevation caused by contamination of the fingertip can occur if capillary samples are obtained.
- Detectable BLLs are associated with irreversible neurocognitive deficits and a lower limit for this toxicity has not been established.
- Many blood lead tests will result below the reference level (5 mcg/dL) but there is no safe lead level.
- In patients with elevated BLLs, screening for iron deficiency anemia should also occur.
  - Red blood cells of unequal size (anisocytosis)
  - Abnormally shaped red blood cells (poikilocytosis)
- Symptoms
  - Vomiting, cognitive impairment, language delay, hearing loss, and behavior problems at low concentrations and colicky abdominal pain, anemia, intellectual disability, seizures, renal insufficiency, and encephalopathy at higher concentrations.
- Treatment
  - Children with BLLs <45 mcg/dL don’t receive chelation therapy
  - A plain abdominal radiograph is warranted in patients with BLL >15 to 44 mcg/dL and pica behaviors (eg, eating paint chips or excessive mouthing) and all patients with BLL ≥45 mcg/dL
  - Chelation therapy
  - Gastric lavage

**Disseminated Intravascular Coagulation (DIC)**
- Pathologic activation of coagulation system
- Widespread microthrombi: consumes coag factors (V, VIII, fibrinogen) & pts
- Severe thrombocytopenia: diffuse bleeding from skin, RT, GIT
- Thrombi decreased blood flow to organs (esp. kidneys)
- Etiologies
  - Infx: gram (-) sepsis endotoxins
  - Malignancies: AML, lung/GI/prostate ca
  - Obstetric: pre-eclampsia, abruption placentae
  - Massive tissue injury & trauma: burns
  - Other: RMSF, liver dz, viral, AA, ARDS
- Symptoms
  - Widespread hemorrhage (venipuncture sites, mouth, nose, extensive bruising)
  - Thrombosis (RF, gangrene, hepatic/resp. dysfxn)
- Diagnosis
  - Increased thrombin formation
  - Dec. fibrinogen
  - Inc. PTT/PT/INR
  - Severe thrombocytopenia
  - Schistocytes on PS
  - Increased fibrinolysis
  - Inc. D-dimer
- Treatment
  - Tx underlying cause
  - Plt transfusion (only if <20K)
  - FFP if severe bleeding (to replace coag factors)
  - Cryoprecipitate (replaces fibrinogen)
  - +/-Heparin for thrombosis (use with caution → pts cycle into bleeding)

**Disorders**

<table>
<thead>
<tr>
<th>Disorders</th>
<th>PT</th>
<th>PTT</th>
<th>Bleeding Time</th>
<th>Platelet Count</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
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<td>Unaffected</td>
<td>Prolonged</td>
<td>Decreased</td>
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<tr>
<td>Hemophilia</td>
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<td>Unaffected (if plt normal)</td>
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<td>Von Willebrand Dz</td>
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<td>Prolonged</td>
<td>Prolonged (esp. ASA challenge)</td>
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<tr>
<td>Vit K Deficiency</td>
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<td>Normal/minor prolongation</td>
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