Hematology Review

April Stouder, MHS, PA-C
NCAPA Winter Conference 2017
Learning Objectives

- Review the PANRE exam blueprint covering anemias, coagulation disorders and malignancies
- For each hematologic condition, outline the following:
  - Pertinent historical information
  - Risk factors
  - Signs and symptoms
  - Physical examination
  - Differential diagnosis
  - Treatment
Hematopoiesis

- Formation of blood cells
  - Under **normal** conditions, production and turnover are coordinated
  - Continuous production
  - Stress = increased production (illness, altitude, exercise, bleeding)
Erythropoiesis

- Requirements include
  - Erythropoietin stimulation of a healthy bone marrow
  - Adequate supply of iron
- Peritubular interstitial cells of the kidney produce Epo in response to lower oxygen delivery
Red blood cells contain several hundred thousand hemoglobin molecules, which transport oxygen.
Classification of Anemia

- Pathophysiologic
  - Production vs destruction problem
  - Make the **distinction by reticulocyte count** (2%)
  - Normal response to anemia = increased reticulocytes

- Morphologic
  - Size matters...look at the MCV
Morphologic Classification

- Microcytic
  - MCV < 80
- Normocytic
  - MCV 80-100
- Macrocytic
  - MCV > 100
Differential Diagnosis for Microcytic Anemia

“TICS”
- Thalassemia
- Iron Deficiency
- Chronic Inflammation (anemia of chronic disease)
- Sideroblastic

Used with permission from Alan Platt, PA-C, Emory PA Program
Differential Diagnosis for Macrocytic Anemia

- “BIG FAT RED CELLS”
  - $B_{12}$ Deficiency
  - Inherited Disorders (rare)
  - GI surgery/illness
  - Folic acid Deficiency
  - Alcoholism
  - Thiamine-responsive anemias (rare)
  - Reticulocytes (false elevation of MCV)

- Endocrine disorders (hypothyroid)
- Dietary Deficiencies
- Chemotherapy drugs
- Erythroleukemia (immature blasts large size)
- Liver Disease
- Lesch-Nyhan syndrome (rare)
- Splenectomy

Used with permission from Alan Platt, PA-C, Emory PA Program
Differential Diagnosis for Normocytic Anemia

• “NORMAL SIZE”
  • Normal pregnancy (30% plasma increase)
  • Overhydration/expansion of plasma volume
  • Renal Disease
  • Marrow infiltration (leukemia, fibrosis, infection)
  • Acute blood loss
  • Liver disease
  • Systemic inflammation (anemia chronic disease)
  • Zero production (red cell aplasia, aplastic anemia)
  • Endocrine disorders (thyroid, adrenal)

Used with permission from Alan Platt, PA-C, Emory PA Program
Iron Deficiency Anemia

- Most common cause of anemia worldwide

- Classically microcytic, although Hgb drops before MCV (early anemia is normocytic)

- Iron deficiency is a SYMPTOM, not a disease
  - Need to unearth the underlying cause
Risk Factors

- Poor diet
  - Children, pregnant women, elderly
- Chronic aspirin or NSAID use
  - GI tract blood loss
- Menorrhagia, malignancy, dialysis, blood donation
  - Increased losses
- Gastric resection, celiac disease
  - Decreased absorption
- Pregnancy, infancy, lactation, adolescence
  - Increased requirements
***Iron deficiency anemia in an adult is due to blood loss, most likely GI, until proven otherwise!!!
Clinical Findings

- None in early disease
- Fatigue, dyspnea on exertion, tachycardia
- Poor weight gain in infants
- Cheilosis, nail changes
- Dysphagia (Plummer-Vinson syndrome)
- **Pica**—ice, starch, clay/dirt
Diagnosis/Lab Findings

- **CBC → Hgb & Hct decreased**
  - MCV low (normal in early stages)
  - Platelets can be elevated (reactive)

- **Peripheral blood smear**
  - No changes early on
  - Microcytic RBCs, anisocytosis, poikilocytosis
Diagnosis / Lab Findings

- Iron Studies:
  - SERUM IRON: LOW
  - TIBC: HIGH
  - SERUM FERRITIN: *LOW

FERRITIN LEVELS REFLECT IRON STORES

**acute phase reactant**
KEY CONCEPT: No clinical situation other than iron deficiency exhibits extremely LOW Ferritin levels
Treatment

- Evaluate & treat blood loss
- Oral iron supplementation
  - Ferrous sulfate 325mg po TID between meals
  - Encourage stool softeners!!
- Parenteral Iron
  - Fail to respond to oral, intolerant, ongoing blood loss, GI disease
- Check CBC in 3-4 weeks, as Hgb normalizes quickly. Up to 6 months to replenish iron stores
Thalassemia

- Hereditary disorders characterized by reduced or absent production of globin chains (α or β)
Hemoglobin Types

- Normal hemoglobin consists of a tetramer of $\alpha_2\beta_2$ (Hgb A)
  - Represents ~ 98% of circulating adult hemoglobin
- Hemoglobin A₂ ($\alpha_2\delta_2$)
  - 1-2% of adult Hgb
- Hemoglobin F ($\alpha_2\gamma_2$)
  - Major Hgb of fetal life
  - Drops off around age 1
  - Less than 1% of adult Hgb
Thalassemia

- Risk Factors
  - Family History
  - Ethnicity

- Suspected in a person with
  - Personal history of lifelong microcytic anemia
    - Doesn’t respond to iron – don’t confuse with Fe Def anemia!
    - **Microcytosis out of proportion to degree of anemia**
    - MCV often less than 70
Alpha Thalassemia

- Commonly seen in **Southeast Asian & Chinese populations**
- Results from α-gene deletion

<table>
<thead>
<tr>
<th>α-globin Genes Present</th>
<th>Disorder</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Silent carrier</td>
<td>No anemia, normal MCV</td>
</tr>
<tr>
<td>2</td>
<td>Alpha thal trait</td>
<td>Mild anemia, microcytic (MCV 70-80)</td>
</tr>
<tr>
<td>1</td>
<td>Hgb H disease</td>
<td>Very microcytic (MCV 60-70), chronic hemolysis, variable anemia</td>
</tr>
<tr>
<td>0</td>
<td>Hydrops fetalis</td>
<td>Incompatible with life</td>
</tr>
</tbody>
</table>
Beta Thalassemia

- Caused by $\beta$-gene mutations rather than deletions
  - Results in reduced or absent $\beta$-chains
  - Excess $\alpha$-chains $\rightarrow$ unstable, causes hemolysis
    - Hemolysis occurs in marrow & circulation

- Primarily affects persons of Mediterranean origin (Italian, Greek)
# Beta Thalassemia

<table>
<thead>
<tr>
<th>Genetic Abnormality</th>
<th>Disorder</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous $\beta^0$</td>
<td>Thalassemia major (Cooley’s anemia)</td>
<td>Severe chronic hemolysis &amp; anemia, transfusion dependent. Bony abnormalities on PE. Iron overload.</td>
</tr>
<tr>
<td>Homozygous $\beta^+$</td>
<td>Thalassemia intermedia</td>
<td>Moderate chronic hemolysis &amp; anemia. Occasional transfusions. Iron overload.</td>
</tr>
<tr>
<td>Heterozygous $\beta^0$ or $\beta^+$</td>
<td>Thalassemia minor</td>
<td>Mild anemia, no PE abnormalities. Rare transfusions.</td>
</tr>
</tbody>
</table>
Clinical Findings

- Thalassemia major- (Cooley’s anemia)
  - Diagnosed in infancy (decreased Hgb F)
    - Anemia is severe (HCT as low as 10%)
    - Transfusion dependent → iron overload
  - Bone marrow expansion → bony deformities
- Growth retardation
- Jaundice, HSM
- Limited life expectancy without effective treatment
Thalassemia Treatment

- Transfuse as needed
  - Caution - risk of iron overload
  - Iron chelation

- Folic acid supplement

- Genetic counseling

- Stem cell transplant – Cooley’s; children – offers chance for cure with HLA matched donor!
Anemia of Chronic Disease

- Organ failure or impaired marrow function
  - Common causes
    - Liver disease, acute or chronic infection (HIV), chronic inflammation (RA, lupus), hypothyroidism, renal disease (diabetic/hypertensive), malignancy

- Reduced erythropoietin stimulation of bone marrow
Clinical Findings

- Usually mild to moderate anemia
  - If more severe anemia, consider
    - Renal disease
    - Co-existing nutritional deficiency

- Signs & Sx usually related to underlying disease process
Diagnosis / Lab Findings

- Diagnosis of exclusion!
- Microcytic (up to 30%) or normocytic morphology
- Normal appearing peripheral smear
- Reticulocytes low
- Inappropriately low erythropoietin level
- Serum iron *and* TIBC may be low, but ferritin is normal or elevated
  - Don’t confuse with iron deficiency!
## Contrasting Fe Def and Anemia of Chronic Disease

<table>
<thead>
<tr>
<th>IRON STUDIES</th>
<th>Iron def</th>
<th>Chronic dz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SERUM IRON</strong></td>
<td>VERY LOW</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>TIBC</strong></td>
<td>*HIGH</td>
<td>*LOW</td>
</tr>
<tr>
<td><strong>SERUM FERRITIN</strong></td>
<td>*LOW</td>
<td>*HIGH</td>
</tr>
<tr>
<td><strong>MCV</strong></td>
<td>mod LOW</td>
<td>mild LOW</td>
</tr>
</tbody>
</table>
Treatment

- Treat underlying disease
  - Anemia often remits
- Unless patient is symptomatic or transfusion dependent, no treatment generally indicated
- Treat any co-existing deficiencies (iron, folate, etc)
- Erythropoietin injections (Procrit, Aranesp) are helpful for certain patients
- Transfusions only if needed
Aplastic Anemia

- **Bone marrow failure**, arising from injury or suppression of hematopoietic stem cell
  - Causes pancytopenia

- Incidence in Western countries is 1-5 cases/million persons/year
  - In US, ~1000 cases diagnosed a year

- Can occur at any age
  - Most common in young adults (20-25) or >60
  - Male = female
Causes

• Acquired
  • Drugs: phenytoin, sulfonamides
  • Chemotherapy, radiation (dose related)
  • Chemicals: benzene, solvents, insecticides
  • Viruses: hepatitis, HIV, EBV
  • Lupus

• Hereditary (rare)
  • Fanconi’s anemia

• Idiopathic—50-65% of cases (likely autoimmune)
Clinical Findings

- Onset abrupt or insidious
- Significant pancytopenia
  - Fatigue / Weakness
  - Dyspnea
  - Excess bleeding/bruising
  - Petechiae, purpura
  - Pallor
  - Infections
- Notably absent are hepatosplenomegaly or lymphadenopathy
Diagnosis / Lab Findings

- **Hallmark = pancytopenia**
- Anemia may be severe
- Decreased reticulocytes
- Morphology and MCV usually normal
- Bone marrow is **hypocellular**, but no abnormal cells
Treatment

- Based on severity of disease
  - If mild, monitor & supportive care
  - Transfusions, treat infections

- Severe disease
  - ANC <500, plts<20K, anemia w/retic <1%

- Bone marrow transplant
  - Only 25-30% of patients will have a matched sibling

- Immunosuppression
  - If not a transplant candidate or without a match
B12 Deficiency

- Vit B₁₂ (cobalamin) is not synthesized by the body, must come from diet
  - Foods of animal origin only
    - Meat, dairy, eggs

- Upon digestion, binds with Intrinsic Factor (IF), secreted by gastric cells
  - B₁₂-IF complex absorbed in terminal ileum & stored in liver
Causes

- Inadequate intake (rare in US)—vegans

- Malabsorption
  - Inadequate production of IF (70%)
    - Pernicious anemia → most common cause
    - Gastrectomy

- Disorder of terminal ileum
  - Celiac, enteritis, resection, neoplasm, Crohn’s
Clinical Findings

- Glossitis
- Pallor
- Anorexia
- Diarrhea
- **Peripheral neuropathy**
  - Stocking-glove paresthesia
  - Loss of position & vibratory sense
  - Ataxia and dementia
  - Permanent if not treated – 6 months
Diagnosis / Lab Findings

- **Classically macrocytic**
  - MCV 110-140
- Anemia may be severe, with coexisting thrombocytopenia and leukopenia
- Peripheral smear: *hypersegmented neutrophils*
- Decreased retic count
- *Serum B12 levels low (normal >240pg/mL)*
  - <170 pg/mL → anemia
  - <100 pg/mL → symptoms
- **Schillings test** rarely used
Treatment

• Mainstay of treatment is replacement therapy
  • Oral or parenteral (IM)
  • Lifelong for pernicious anemia, resection of ileum, gastrectomy, strict vegans

• Response is brisk
  • Normal CBC in 2 months
Folate Deficiency

- Fruits and vegetables = primary dietary source

- Common causes
  - Poor diet
  - Alcoholics, elderly
  - Increased requirements
    - Hemolysis, pregnancy, dialysis, infancy
  - Malabsorption → rare
Clinical Findings

- Malnourished appearing
- Diarrhea
- Cheilosis
- Glossitis

**Neurological symptoms do NOT occur**
Diagnosis / Lab Findings

- Lab findings very similar to B12 deficiency
  - Macrocytosis
  - Howell-Jolly bodies
  - Normal B12 levels

- RBC Folate level <150 ng/mL is diagnostic
  - RBC folate is better than serum folate
    - not subject to fluctuations based on intake
Treatment

- Oral replacement therapy with Folic acid
  - 1 mg daily
  - Parenteral folate is rarely necessary
- Brisk response
  - 1-2 months
- Duration of therapy depends on cause of deficiency
  - ie, hemolytic anemia will need indefinitely
Hemolytic Anemias

- Group of disorders in which RBCs are destroyed, either episodically or continuously
  - If bone marrow is not able to keep up with rate of destruction $\rightarrow$ anemia
  - Bone marrow has the ability to increase RBC production significantly to respond to losses
    - Reflected by *reticulocytosis*
Classification

- RBC destruction
  - intrinsic defect of the cell
  - some external factor

- Intrinsic abnormalities: problems with membrane, enzyme defects, hemoglobin
  - Usually hereditary

- Extrinsic factors: autoimmune, drugs, infection or trauma
  - Often acquired
Differential Diagnosis of Hemolytic Anemia

- “HEMATOLOGIST”
  - Hemoglobinopathies
  - Enzyme deficiency
  - Medications (sulfa, hi-dose PCN)
  - Antibodies
  - Trauma to RBCs
  - Ovalocytosis—inherited d/o in SE Asians
  - Liver disease, severe
  - Osmotic fragility—spherocytosis, elliptocytosis (hereditary)
  - G-6PD deficiency
  - Infection (parasite, bacterial)
  - Splenic destruction
  - Transfusion—acute or delayed

Used with permission from Alan Platt, PA-C Emory PA Program
Glucose-6-Phosphate Dehydrogenase Deficiency

- Hereditary enzyme defect causing episodic hemolysis
  - X-linked recessive disorder seen in about 11% of AA men in US & some Mediterranean populations
  - Absence of G6PD enzyme makes RBC sensitive to oxidation
  - Oxidized Hgb forms precipitate called Heinz body
    - Damages RBC membrane
    - Leads to removal by spleen (bite cells)
Clinical Findings

- Usually healthy
- Female carriers rarely affected
- No splenomegaly
- *Episodic hemolysis* often triggered by oxidative stress
  - Acute infections
  - Acidosis
  - Drugs (sulfa, antimalarials, ASA)
  - Fava beans
- Episodes usually self-limited