Anemia in Women
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What is blood?

- **Plasma (60%)**
  - Water
  - Dissolved ions and protein

- **Cellular components (40%)**
  - WBCs
  - RBCs
  - Platelets
Erythrocyte Development

1. Stem cell
2. Early RBC progenitor
3. Late RBC progenitor
4. Pronormoblast
5. Basophilic normoblast
6. Polychromatophil
7. Orthochromatrophic normoblast
8. Reticulocyte (large cell)
9. Mature RBC
What are reticulocytes?

Adolescent RBCs
1. Erythropoietin from kidneys
2. Bone marrow responds
3. Reticulocytes are produced
4. Released into circulation

Accelerated RBC production ➔ more reticulocytes!
What accelerates RBC production?

1. Hemolysis
2. Blood loss
3. Hemoglobin S disease
4. Cancer
5. Pregnancy
6. Iron replacement in iron deficiency anemia
What if reticulocytes are decreased?

- Normal
  - 1-2% of RBCs are reticulocytes

- Decreased when bone marrow is not making RBCs
  - Iron deficiency
  - Aplastic anemia
  - Chronic infection
  - Untreated pernicious anemia
What is hemoglobin?

- Oxygen carrying protein
- 2 pairs of polypeptide chains (globins)
  - 2 alpha chains
  - 2 beta chains
- Each chain has heme molecule
  - Heme = iron + protoporphyrin
- Hemoglobinopathy
  - Abnormal hemoglobin
Types of Hemoglobin (Hb)

Fetal hemoglobin
  – Hb F

Hb A
  – Adult hemoglobin
  – 2 alpha and 2 beta chains

Hb A₁c
  – Hb A with glucose
  – 3-6 % normal
  – Elevated with diabetes
Hemoglobinopathy

- Sickle cell
  - Hb S – beta chain mutation
  - Most common hemoglobinopathy
- Thalassemia
  - Deletion or mutation of \( \alpha \) chain
Red Blood Cell Indices

- RBC
- Hgb
- Hct
- MCV
- MCH
- MCHC
- RDW
- Reticulocytes
Red Blood Cell Count (RBC)

- Number of RBCs/cubic ml
- 3.6-5.0 x 10^6/ml
- Lower in recumbent position
- Exercise/excitement increase
- Dehydration increases
Hemoglobin (Hb)

- Amount of hemoglobin in blood
- 30% of RBC is Hb
- 12-16 g/dL
Hematocrit (Hct)

- Volume of RBCs
- Immediate acute loss
  - Equilibrium occurs
  - HCT will not reflect blood loss
- 37-47% by venipuncture
- 42-44% by finger stick
Mean Corpuscular Volume (MCV)

- Average volume of single RBC
- Classifies anemia
  - Microcytic
  - Normocytic
  - Macrocytic
- 80-100 (10^7) fl/L
- 80-83 low normal
Mean Corpuscular Hemoglobin (MCH)

- Average weight for each RBC
- Picograms
- 26-34 pg
- Not used as much as others
Mean Corpuscular Hemoglobin Concentration (MCHC)

- Average hemoglobin concentration
- 31 g/ 37 dL
Red Cell Distribution Width (RDW)

- Coefficient of variation of red cells
- Anisocytosis
  - Variation in cell size
- Normal 11.5-14.5
Reticulocytes

- Number of immature RBCs
- May increase MCV (large cells)
Other RBC Indices

- Serum Ferritin
- Serum Iron
- Total Iron Binding Capacity
- Transferrin Saturation
- Serum Folate
- Serum Vitamin B-12
Serum Ferritin
Body’s Storage of Iron

- Low serum ferritin
  - Iron deficiency
  - First abnormal indice with iron deficiency
- Normal serum ferritin
  - Chronic disease
- Increased serum ferritin
  - Iron overload
  - Inflammatory diseases
  - Alcoholism
Iron Indices

- **Transferrin**
  - Protein that transports iron
  - Measured by total iron binding capacity (TIBC)

- **Serum Iron**
  - Amount of iron bound to transferrin

- **Transferrin saturation**
  - Percentage of serum iron to TIBC
  - 20-50%
Red Blood Cell Folate

- Diagnose macrocytic anemia
- Low folate
  - Folate deficiency
  - Must be low for > 20 weeks to change cells
  - Pancytopenia?
- Low RBC folate
  - Specific for folic acid deficiency
Serum B-12

- Low B-12
- Diagnose macrocytic anemia
Classification of Anemia by Etiology

- Decreased healthy RBC production
  - Bone marrow does not produce enough cells
  - Maturational defect in cells
Classification of Anemia by Etiology

- Increased RBC loss
  - Blood loss
- RBC destruction
  - Intrinsic (sickle cell)
  - Extrinsic (mechanical cardiac valve)
- Combination of above
Classification by RBC Morphology

Size

- Microcytic: decreased MCV
- Normocytic: normal MCV
- Macrocytic: increased MCV

Color

- Normochromic
- Hypochromic
Microcytic Anemias

- Iron deficiency
- Thalassemia
- Anemia of chronic disease
Macrocytic Anemias

- Megaloblastic
  - Vitamin B-12 deficiency
  - Folate deficiency
- Non megaloblastic
  - Chemotherapy
  - Liver disease
  - Reticulocytosis – excess of immature cells
  - Myxedema - chronic hypothyroidism
Normocytic Anemias

- Acute blood loss
- Anemia of chronic disease
- Infection
- Medications
Signs and Symptoms of Anemia

- Often asymptomatic
- Systolic murmur
- Hypotension
- Glossitis
- Chilitis
Signs and Symptoms of Anemia

- Dry skin
- Thin hair
- Pallor
- Nail ridges
- Pale conjunctiva
Microcytic Anemia
Iron Deficiency Anemia

Most common anemia
Normal Iron Metabolism

Ferritin: stored iron
- 30% of total body iron
- Found in liver, spleen, and bone marrow

Transferrin
- Transfers iron from storage to functional pool
Normal Iron Metabolism

- Transferrin recognized by target tissues via a specific receptor
- Cells with greater iron need express greater number of receptors
- Iron internalized by endocytosis
Normal Iron Metabolism

- Apoferritin traps iron as part of storage complex (ferritin)
- Erythropoietin secreted by kidneys
  - Stimulates RBC production
## Lab Findings

<table>
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<th>Folate</th>
<th>Iron</th>
<th>Chronic Disease</th>
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<td>MCHC</td>
<td>→</td>
<td>→</td>
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<td>↓/→</td>
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<tr>
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<td>macrocytic</td>
<td>macrocytic</td>
<td>microcytic</td>
<td>normocytic</td>
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</table>
Lab Values

Smear

– Hypochromic
– Microcytic
– Anisocytosis
  - Ani – Greek for unequal
  - Abnormal sizes of RBCs
– Poikilocytosis
  - Poikolo – Greek for irregular
  - Abnormal shapes of RBCs
Lab Values

- Serum ferritin
  - <15 mcg/L
- TIBC
  - Rises
- Serum iron
  - <30 mcg/dL
- MCV
  - <80
- MCHC
  - <30
- RDW
  - Elevated
Evaluation of Iron Status

- Serum Ferritin
  - Indicates total body iron stores
  - < 15 mcg/L deficiency
  - Increase
    - Systemic inflammation
    - Infection
    - Liver disease
Evaluation of Iron Status

- **Transferrin Saturation**
  - \( \frac{\text{Serum iron}}{\text{total iron binding capacity (TIBC)}} \)
  - Saturation < 20% indicates deficiency
Signs and Symptoms

- Fatigue
- Tachycardia
- Shortness of breath
- Left ventricular hypertrophy
- Angina
Iron Deficiency Anemia

30% of Diagnosed Anemia

- Inadequate intake
- Malabsorption
- Excessive blood loss
  - Menstrual
  - GI
- Increased requirements
  - Pregnancy or lactation
Differential Diagnosis

- Anemia of chronic disease
  - Normal or elevated ferritin
- Thalassemia
  - More microcytosis
  - Normal iron parameters
- Iron deficiency responds to iron therapy
Oral Iron Therapy

Iron dose (adults)
- Recommended dose = 200mg/day
- Duration = 3 months
- Will respond in 10 - 21 days

Ferrous sulfate preferred
- Adverse effects
  - GI complaints
Comparison of Oral Products

<table>
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<tr>
<th>Product</th>
<th>% Iron</th>
<th>Daily dose</th>
<th>Fe/day</th>
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<tr>
<td>Ferrous sulfate</td>
<td>20%</td>
<td>325mg tid</td>
<td>195mg</td>
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<tr>
<td>Ferrous fumarate</td>
<td>33%</td>
<td>200mg tid</td>
<td>198mg</td>
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<tr>
<td>Ferrous gluconate</td>
<td>11%</td>
<td>600mg tid</td>
<td>198mg</td>
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</table>
Administration of Oral Iron

- Empty stomach if no GI distress
- Administer with meat, fish, or Vitamin C foods
- Keep out of reach of children
Parenteral Iron Therapy
(Iron Dextran)

- Noncompliance or malabsorption
- Single dose IV
  - Dose: 500-3000 mg
  - Iron content = 50mg/ml
  - Total mg Iron = \[0.0442 \times (\text{desired Hgb-Obs Hgb}) \times \text{IBW} + (0.26 \times \text{IBW})\] \times 50
Iron-Rich Foods

- Animal protein
  - Heme iron
- Deep green vegetables
- Iron-fortified cereals
Parenteral Iron Therapy
(Iron Dextran)

Side effects - anaphylaxis
- Arthralgia
- Myalgia
- Flushing
- Malaise
- Fever
- Allergy/anaphylaxis

Give test dose: 25mg (0.5ml)
Follow-Up

- Repeat CBC 2-4 weeks after therapy initiated
- If no response
  - Evaluate for other anemia
Anemia of Chronic Disease

- Microcytic anemia
- Normocytic/normochromic anemia
- 25% of all diagnosed anemia
Chronic Diseases Causing Anemia

- Chronic infection or inflammation
- HIV
- Cancer/malignancy
- Liver failure
- Chronic renal failure
  - Decreased erythropoietin
Clinical Findings

- Signs and symptoms of anemia
- Labs
  1. Low serum iron
  2. Low TIBC
  3. Normal or increased serum ferritin
- Dialysis
  1. Low folate
- GI blood loss
  1. Positive guaiac
Further Lab Findings

1. Hct rarely below 25%
   (Except with renal failure)
2. MCV normal or slightly low
3. RBC morphology normal
4. Reticulocytes normal/low
5. Serum ferritin normal/low
6. Serum iron low
7. Transferrin saturation very low
Common Features

- Hypo-proliferative bone marrow
- Low serum erythropoietin
Goals of Therapy

- Increase Hct to target 30% to 36%
- Decrease morbidity and mortality
- Decrease transfusion requirements
Erythropoietin

- 50-100U/kg TIW, IV or SC
- Reduce dose when:
  1. HCT approaches 36%
  2. HCT increases > 4 points in 2 weeks
- Increase dose when:
  1. Hct does not increase > 5-6 points after 8 weeks
  2. Hct is below target
Side Effects

- Hypertension (25%)
- Arthralgia
- Nausea
Factors Decreasing Response to Therapy

- Iron deficiency
- Blood loss
- Infection
Iron Supplementation with Erythropoietin

May be PO or IV
- PO: 200mg elemental iron daily
- IV: 100mg for 10 consecutive treatments

Avoid enteric-coated formulations
Lead Poisoning

Microcytic Anemia
Lab Findings

- Hb 8-13 or lower
- HCT 20-30%
- Low MCV
- Low MCHC
- Slightly elevated reticulocytes
- Smear dimorphic
  - Normal cells
  - Hypochromic cells
  - Coarse basophilic stippling
- Elevated lead levels
Symptoms Chronic Toxicity: Serum Lead 25-50 mcg/dl

- Dark line (lead sulfide)
  - Gums around the teeth
- Abdominal pain
- Constipation
- Vomiting
- Peripheral neuropathy
- Muscle weakness
Legal Aspects

- Notify OSHA and remove worker
  1. Serum lead > 60
  2. Serum lead > 50 x 3
- Severe poisoning
  1. Coma
  2. Convulsions
  3. Serum lead > 70
Thalassemia

Autosomal Recessive Disorder
Thalassemia

- Microcytosis out of proportion to degree of anemia
- Lifelong
- Family history
- Abnormal RBC morphology
  - Microcytes
  - Acanthocytes
  - Target cells
Thalassemia

- Alpha and beta thalassemia
- Genetic mutations
- Occur in areas where malaria was endemic
Alpha Thalassemia

China, Philippines
Malaysia, Thailand,
Cambodia, Laos,
Vietnam, Burma,
India, Sri Lanka,
African and American
blacks
Alpha Thalassemia

- Silent carrier
- Thalassemia minor
- Hemoglobin H disease
- Hydrops fetalis
  - Incompatible with life
Silent Carrier

- 3 alpha globulin genes, 1 alpha globulin gene affected
- Normal hematocrit
- No clinical or hemoglobin abnormality
- Can only be detected by DNA studies
- No treatment
Alpha Thalassemia Minor (Trait)

- 2 alpha globulin genes normal
- 2 alpha globulin genes affected
- Hct 32-40%
- Hgb normal or decreased
- RBC normal or increased
- MCV below 80
- MCH below 26
Alpha Thalassemia Minor

- Normal hemoglobin electrophoresis
- RBC morphology
  - Microcytosis
  - Hypochromic
  - Aniso/poilokocytosis
- Iron studies normal
- Remember may have a combination of anemias!
Alpha Thalassemia Minor in Pregnancy

- Non-black
  - Screen father of the baby

- Black population
  - Alpha thalassemia major not possible

- Consult for maternal Hb below 10

- If present in both parents
  - Refer for genetic counseling
Hemoglobin H Disease

- One alpha globulin gene normal
- Three alpha globulin genes affected
- Hct 22-32
- Hgb 7-10
- MCV <26
- MCH <80

- Reticulocytosis
  - 5-10%
- Microcytosis
- Hypochromia
- Targeting
- Misshapen red cells
- Hgb electrophoresis
  - 5-30% Hgb H
Symptoms of Hb H Disease

- Hepatosplenomegaly
- Gallstones
- Transfusion-dependent
- Milder in blacks
- Anemia worse during pregnancy
- Refer to physician
- Counseling needed
Alpha Thalassemia Major

- No alpha globin genes are normal
- Hydrops fetalis present
- Does not survive
Beta Thalassemia

- Point mutations rather than large deletions
- Beta0 or Beta+
- Alpha chains unstable
- People of Mediterranean origin
  - Greeks 1:10
  - Italians 1:10
  - Asians 1:25
  - American blacks 1:50
Beta Thalassemia

- **Thalassemia major**
  - Homozygous B0 or B+
  - <10% Hgb A

- **Thalassemia intermedia**
  - Mild Homozygous B+
  - < 30% Hgb A

- **Thalassemia minor**
  - Heterozygous B0
  - Heterozygous B+
  - 80-95% Hgb A
Thalassemia Major

- Severe hemolytic anemia
- Regular transfusion program
- Iron overload (hemosiderosis) common
- Shortened life span
Thalassemia Intermedia

- Blacks may have milder clinical course
- Refer to physician for care
Thalassemia Minor

- Heterozygotic
- Lifelong microcytic, hypochromic anemia
- Severe anemia unusual
- May be asymptomatic
- Splenomegaly?
Thalassemia Minor

- MCV < 80
- MCH < 26
- Abnormal peripheral smear
- Elevated Hgb F?
- No treatment needed
Thalassemia Minor

- If pregnant, screen father of baby
- Genetic referral if father has hemoglobinopathy
- If coexistent iron deficiency
  - Treat according to protocol
Sideroblastic Anemias

“Sidero” is Greek for Iron
“Blast” is an immature cell
RBCs without Iron
Sideroblastic Anemias

- Can not incorporate iron into RBC
- Lack enzyme
- Genetic, idiopathic, or acquired
  - Drugs or Toxins
- Ringed sideroblasts present in marrow
  (Nucleated, immature RBC with iron granules)
- Hgb 6-10
- Microcytic, normochromic or normocytic, normochromic
$B_{12}$ and Folate Deficiency

Macrocytic Anemias
Vitamin B₁₂

- Only source is diet
- 3-5 years before deficiency apparent
  - Diet deficiency seen only in vegans
- Bound to intrinsic factor
- Transported to plasma
- Transcobalamin II needed to reach cells
Vitamin $\text{B}_12$ Deficiency

- Decreased production of intrinsic factor
  - Pernicious anemia
  - Gastrectomy
Vitamin B$_{12}$ Deficiency

- Decreased absorption of B-12
  - Fish tapeworm
  - Blind loop syndrome
  - Surgical resection
  - Cohn's disease
  - Pancreatic deficiency

- Inadequate intake (rare)
Clinical Findings

- Weakness
- Weight loss
- Beefy red tongue (glossitis)
- Numbness
- Ataxia
- Memory loss
- Pallor
- Paresthesias
- Decrease reflexes
- Depression
- Decreased vibration or position sense
Diagnosis

- MCV 110-140
- MCV may be normal in presence of another microcytic anemia
- Macro-ovalocytes, multi-lobed neutrophils
- Diagnosed through serum B-12 < 100 pg/L
  - Shilling test
    - Decreased absorption of B-12
- Differentiate from folate deficiency
B_{12} Deficiency

- Gradual development over 1-3 years
- Treatment (Cyanocobalamin)
  - LD: 100mcg/d IM x 3-5 days
  - MD: 100mcg IM q2-4 weeks
B$_{12}$ Deficiency

Response rate

- Reticulocytes and RBCs
  - Similar to iron deficiency
- Neurologic signs and symptoms
  - 6-12 months (If less than 6 months duration)
- Other signs and symptoms
  - 1-2 weeks
Folate Deficiency

- Clinical findings: similar to B12 deficiency
- No neurologic findings
- Macro-ovalocytes
- Hypersegmented neutrophils
- Normal serum $B_{12}$
- Reduced folate
Folate Deficiency

- **Daily requirements**
  - 50-100 mcg

- **Dietary deficiency most common cause**

- **Diagnosis**
  - RBC folate test of choice

- **Gradual development of anemia**
  - 1-5 months

- **Treatment**
  - 1mg/day po x 2-3 weeks
Causes of Folate Deficiency

- Dietary deficiency
- Decrease absorption
  - Topical sprue
  - Drugs
    - Phenytoin, Sulfas
Causes of Folate Deficiency

- Increased requirement
  - Chronic hemolytic anemia
  - Pregnancy
  - Exfoliative skin disease
- Loss of folate
  - Dialysis
- Inhibition of reduction to active form
  - Methotrexate
Other Causes of Macrocytosis

- HIV treated with zidovudine
- Hypothyroidism
  - Mild macrocytosis
- Alcoholism
  - Folate deficiency and liver disease
  - Target cells in peripheral blood
Sickle Cell Trait

Autosomal Dominant Anemia
Sickle Cell Trait

- One gene normal hemoglobin
- One gene for hemoglobin S
- 34-54% hemoglobin S
- Rarely anemic
- Blacks - 8%
- Also in Africans, Italians, Indians
Associated Conditions

- Bacteruria
- Hematuria
- Hyposthenia
  - Diminished strength
- Splenic infarction
  - High altitude
Symptoms

- Generally asymptomatic
- History of bladder/kidney infections
- May confuse diagnosis of other coexisting anemia

Diagnosed by Hb electrophoresis
- 34-54% Hb S
- Sickledex positive
- Normal iron studies
Plan of Care

1. Screen all black pregnant women
   – If positive for trait, screen father of baby
2. No treatment needed for trait alone
3. Pregnant women with sickle cell trait
   – Urinalysis and culture each trimester
   – Educated on S/S UTI
   – Genetic counseling if father has hemoglobinopathy
Image acknowledgments:

- Black, McKay, Braude, Jones, & Margesson (2002)
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