Approach to Anemia

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Normal Red Cell Production
(Erythropoiesis)

Kidney

Bone marrow

Multi-potent stem cell

Erythroid stem cell

3-4 days

Peripheral blood

RBC survival 100-120 days

Blood vessel

Epo mRNA

Epo

Oxygen sensor

100-120 days

3-4 days

Multi-potent stem cell

Erythroid stem cell

Blood vessel

Epo mRNA

Epo

Oxygen sensor

Peripheral blood

RBC survival 100-120 days
Laboratory Evaluation of Anemia

- Complete blood count (including MCV)
- Peripheral blood smear
- Reticulocyte count
  - Relative reticulocyte count
    - Percent of all RBC (normal 0.8%–1.5%)
  - Absolute reticulocyte count
    - Relative reticulocyte count x RBC count
    - Normal 50,000–75,000/µl
- Other workup depending on the suspected causes (i.e. nutritional deficiency, hemolysis, etc)

Anemia

- Low/normal reticulocyte count
  - Decreased production
  - Nutritional deficits
  - Bone marrow pathology
  - I will discuss

- High reticulocyte count
  - Increased loss/destruction
    - Blood loss
    - Hemolysis
  - Dr. Desai will discuss
Anemia with low/normal reticulocyte count

- Low MCV (microcytosis)
  - Iron deficiency
  - Anemia of chronic disease
  - Lead intoxication
  - Sideroblastic anemia
- Normal MCV
  - Anemia of chronic kidney disease
  - Medications
  - Infections
- High MCV (macrocytosis)
  - Vitamin B12 and/or folate deficiency
  - Medications
  - Liver disease, ETOH
  - Thyroid disease

Iron Intake

- Mean iron intake 10-15 mg/d
- Main source of iron intake is meat (especially red meat)
- Serum iron is NOT a marker of iron status (will change with even just one meal)

Contribution of food groups to the iron intake 1992-3

- Bread 11%
- Cereals 39%
- Vegetables 16%
- Meat 15%
- Eggs 3%
- Other 16%

Fairweather-Tait S.; Proc Nutrition Society, 200;63:519-528
## Body Iron Distribution and Storage

- **Duodenum absorption:** ~1-2 mg a day
- **Iron loss (sloughed mucosal cells, menstruation, other blood loss):** ~1-2 mg a day
- **Total body iron storage:** 3000-4000 mg
  - Plasma transferrin: 3 mg
  - Muscle (myoglobin): 300-500 mg
  - Bone marrow: 300 mg
  - Reticuloendothelial macrophages: 600 mg
  - Circulating erythrocytes (Hgb): 1800-2500 mg
  - Liver (storage iron as ferritin): 1000 mg


## Causes of Iron Deficiency in Adults

*Iron deficiency is a symptom, not a disease*

- **A world-wide problem**
  - 3% of toddlers age 1-2 years
  - Up to 10% of women of child bearing age

- **Increased iron requirements**
  - Blood loss
    - Gastrointestinal tract
    - Menstrual periods
    - Blood donation
  - Pregnancy and lactation

- **Inadequate iron supply**
  - Insufficient dietary iron
  - Impaired iron absorption
    - Gastric (bariatric) surgery
    - Atrophic gastritis
    - Intestinal malabsorption
    - Celiac disease
    - *H. pylori* infection
Neurologic syndromes associated with iron deficiency

- **Pica**
  - Latin word for *magpie*, a bird which is reputed to eat almost anything
  - Definition: Compulsive ingestion of a non-food substance such as starch, clay, earth, ice
  - Ceases within days of therapy
  - Occurs in ~25% of patients with iron deficiency anemia from any cause
  - More commonly in women

- **Restless leg syndrome**
  - Common neurologic disorder
  - Criteria for diagnosis:
    1. An urge to move the legs usually accompanied by uncomfortable sensations
    2. Sensation begins or worsens during periods of rest
    3. Sensations relieved by movement
    4. Worse in the evening/night
  - Occurs in ~10% of cases of iron deficiency anemia

Diagnosis of Iron Deficiency

- **Laboratory Tests**
  - Serum ferritin is the best value for iron deficiency (< 20 ug/L diagnostic of Fe deficiency anemia)
  - MCV- the second most reliable indicator of iron stores
  - TIBC- high in iron deficiency and low in ACD
  - Serum iron/iron saturation
    - Doesn’t differentiate between iron deficiency and anemia of inflammation

- **Peripheral blood smear**

![Peripheral blood smear](https://example.com/Peripheral_blood_smear.png)

Ed Uthman from Houston, TX, USA (CC BY 2.0)
Treatment With Iron: Principles

- Iron is absorbed best on an empty stomach
- Ascorbic acid increases absorption and toxicity
- Reticulocytosis occurs <7 days; Increased Hgb in 2-3 weeks
- Maximum iron dose ~200 mg/day
- Side effects: GI upset, constipation, black stool
- Encourage iron rich food

Available Oral Iron Supplements

<table>
<thead>
<tr>
<th>Oral iron preparations</th>
<th>Typical dose (mg)</th>
<th>Elemental iron (mg)</th>
<th>Approx. cost to give 5000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate (also has elixir version)</td>
<td>325 mg tid</td>
<td>65</td>
<td>$10.00</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300 mg tid</td>
<td>36</td>
<td>$7-8.00</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>100 mg tid</td>
<td>33</td>
<td>$8.00-9.50</td>
</tr>
<tr>
<td>Iron polysaccharide complex</td>
<td>150 mg bid</td>
<td>150</td>
<td>$11.00</td>
</tr>
<tr>
<td>Carbonyl iron</td>
<td>50 mg tid</td>
<td>50</td>
<td>$18.00</td>
</tr>
</tbody>
</table>
Inadequate Response to Oral Iron

- Intolerance/Noncompliance (~30% discontinue)
- Persistent blood loss
- Decreased iron absorption
- Chronic inflammation or bone marrow damage
- Chronic kidney disease

IV Iron Agents

- Iron Dextran
  - \textit{INFeD}\textsuperscript{®}
  - \textit{Dexferrum}\textsuperscript{®}
- Sodium ferric gluconate complex (SFGC)
  - \textit{Ferrlecit}\textsuperscript{®}
- Iron Sucrose
  - \textit{Venofer}\textsuperscript{®}
- Ferumoxytol
  - \textit{Feraheme}\textsuperscript{TM}
Anemia of Chronic Disease

- Characteristics
  - Immune-driven by inflammatory cytokines
  - Diversion of iron into RE system (iron not in the “right place”)
  - Blunted erythropoietin response

- Diagnosis - iron status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anemia of Chronic Disease</th>
<th>Iron deficiency anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Iron</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>TIBC</td>
<td>Reduced-Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>% saturation (TSAT)</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Normal-increased</td>
<td>Reduced</td>
</tr>
<tr>
<td>sTfR</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Cytokine levels</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>


- Impaired iron transfer from reticuloendothelial macrophages and duodenum to plasma transferrin, then to liver
### Treatment Options for Anemia of Chronic Disease

- Treat the underlying diseases
- RBC Transfusions
- For anemia of chronic kidney disease:
  - Erythroid-stimulating agents (ESA) and potentially iron supplementation (ferritin <100 and/or iron sat <20%)
- For selected cases of anemia related to cancer or myelodysplatic syndrome
  - Consider ESA

### Megaloblastic Anemia

- Defect in DNA synthesis
- RNA synthesis is relatively unimpaired
  - RBC’s hemoglobin production is far ahead of nuclear maturation
  - Nuclear cytoplasmic dissociation
- Ineffective erythropoiesis
  - Intramedullary hemolysis
  - Decreased red cell survival/misshapen cells
# Vitamin B12 and folate

## Vitamin B12
- **Sources:** dietary meat products
- **Daily requirement:** 2-5 ug/day
- **Total body stores:** 2-4 mg
- **If intake stops, takes 2-3 years for storage to be depleted**

## Folate
- **Sources:** green leafy vegetables
- **Daily requirement:** about 50-100 ug/day
- **Total body reserves:** (5-10 mg) last only 3-4 months
- **Heat labile and water soluble**
- **Absorbed in jejunum and ileum**

## Signs/Symptoms of B12 Deficiency
- **Anemia, hypersegmented neutrophils**
- **“Beefy Red” tongue, smooth surface of the tongue**
- **Neurologic**
  - demyelination of the posterior and lateral columns of the spinal cord
  - paresthesia, loss of position/vibratory sense
  - in advanced disease, neuropathy, muscle weakness, and even CNS symptoms (irritability, somnolence, psychosis)

Bone marrow process

- Broad DDx, including
  - Acute or chronic leukemia
  - Myelodysplastic syndrome (MDS)
  - Myeloproliferative diseases (MPD)
  - Involvement of malignancies in the bone marrow
  - Disseminated infections in the bone marrow
- Patients usually have more symptoms such as unexplained weight loss, petechiae, fever, hepatosplenomegaly, etc
- More than one cell line is abnormal and could be severe
- Referral to hematology and bone marrow biopsy is needed for definitive diagnosis

http://www.uptodate.com/contents/evaluation-of-bone-marrow-aspirate-smears?topicKey=HEME%2F4434&elapsedTimeMs=0&source=search_result&searchTerm=leukemia+bone+marrow&selectedTitle=1%7E150&view=print&displayedView=full

Approach to Anemia

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Classification of Inherited Diseases of Hemoglobin

- Production abnormalities (Thalassemias)
- Structural abnormalities (Hemoglobinopathies)

Alpha-thalassemia

Main mechanism is whole gene deletion:

<table>
<thead>
<tr>
<th>genotype</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>αα/αα</td>
<td>Normal</td>
</tr>
</tbody>
</table>
| -α/αα    | Silent carrier  
SE Asia, 28% African Americans.  
Normal or slightly ↓MCV; ± HbH inclusions |
| -α/-α    | α-thalassemia minor  
SE Asia, 3% of Black Americans,  
Mediterranean |
| -/-αα    | No clinical disease  
No or mild anemia, ↓MCV, target cells  
HbH inclusions may be seen  
Genetic counseling |
### Beta-thalassemia

- Hypochromic, microcytic anemia
- Variants Major, Intermedia, Minor
- ↑ WBC, normal platelet count
- Iron studies - ↑ serum Fe, transferrin saturation and ferritin
- Bone marrow – erythroid hyperplasia
- Hemoglobin electrophoresis
  - Minor – elevated HbA2
  - Only HbF and HbA2 are present
  - Variable amounts of HbA if transfused

### Anemia with high reticulocyte count

- Low MCV (microcytosis)
  - Hemoglobinopathies (such as some sickle cell)
- Normal/High MCV
  - Acute hemorrhage
  - Hemolytic Anemia
    - Hemoglobinopathies
    - Membranopathies/enzymopathies
    - Autoimmune
    - Microangiopathic Hemolytic Anemia
Unstable Hemoglobins

• Rare disorders. Many variants described
• Autosomal dominant only heterozygotes exist (homozygous do not survive)
  • Disrupt contact between heme and globin
  • Alter amino acids at interface between $\alpha$ and $\beta$ chains
  • Alter the shape or structure of the globin molecule

Unstable Hemoglobins

• Denaturation and precipitation of globin chains in RBC’s $\rightarrow$ Heinz bodies which cling to membrane $\rightarrow$ removed in spleen $\rightarrow$ hemolysis
### The Common Variants of Sickle Cell Disease

<table>
<thead>
<tr>
<th>Name</th>
<th>Genotype</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous SS <em>(Sickle Cell Anemia)</em></td>
<td>$\beta^s - \beta^s$</td>
<td>65</td>
</tr>
<tr>
<td>Heterozygous SC</td>
<td>$\beta^s - \beta^c$</td>
<td>24</td>
</tr>
<tr>
<td>Heterozygous S-(\beta^+) thal</td>
<td>$\beta^s - \beta^+) thal</td>
<td>7</td>
</tr>
<tr>
<td>Heterozygous S-(\beta^-) thal</td>
<td>$\beta^s - \beta^-) thal</td>
<td>3</td>
</tr>
</tbody>
</table>

### Sickle Cell Anemia Pathophysiology

- Manifestations of SCD are driven by:
  - Vaso-occlusion with ischemia-reperfusion injury
  - Hemolytic anemia
  - Endothelial Activation

*Owusu-Ansah 2015*
Mortality in Sickle Cell Disease

Childhood mortality rates in SCD

- In 1973 – median survival of 14.3 years
- CSSCD ~ 85% SS children and adolescents with survived to age 20
- In 2004 survival analysis of SS and Sβ° subjects SCD-related survival 93.6% by age 18


Complications of SCD

Sepsis
Priapism
Myocardial Infarction
Multiorgan Failure
Transfusion Reaction

# Immune Hemolytic Anemias

- Autoimmune
  - Warm antibody-mediated
  - Cold antibody-mediated
  - Paroxysmal Cold Hemoglobinuria
- Drug-related hemolysis
- Hemolytic transfusion reactions
- Hemolytic disease of the newborn
- Paroxysmal Nocturnal Hemoglobinuria

## Auto-Immune Hemolytic Anemias

- Antibodies causing hemolysis can be broken down into 2 general categories: warm and cold
- Warm antibodies react with RBCs best at 37° and typically do not agglutinate red cells
- Cold antibodies typically react best at <32° and do cause RBC agglutination
Coomb’s Test

- The Direct Coomb’s = DAT (Direct Antiglobulin Test) - tests for IgG or C3 DIRECTLY ON THE RED CELLS.
- The Indirect Coomb’s - tests for IgG or C3 in the serum which react with generic normal red cells. This is also known as the antibody screen in blood-banking.

Warm-Antibody Hemolytic Anemias Etiology

- Primary or Secondary
  - Drugs
  - Solid or hematologic malignancy
  - Infection
  - Collagen Disease
  - Pregnancy
- Can be associated with immune platelet destruction = Evan’s syndrome
**Warm-Antibody Hemolytic Anemias Clinical Features**

- Splenomegaly, jaundice is usually present
- Depending on degree of anemia and rate of fall in hemoglobin, patients can have VERY symptomatic anemia
- Lab Dx -
  - ↑reticulocytes, ↑bili, ↑LDH, ↓haptoglobin
  - Positive Coomb’s test - both direct and indirect
  - Spherocytes are seen on the peripheral smear

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**Warm-Antibody Hemolytic Anemias Treatment**

- Patients may require red cell transfusions, if they are symptomatic with their anemia
- However, immunosuppression is the mainstay of therapy
- First Line – Steroids
  - 1mg/kg/d prednisone oral or methylprednisolone IV
  - Continue until Hb > 10g/dL then taper
  - Continue with Vitamin D, Ca, + bisphosphonates
  - Consider PCP prophylaxis
  - Supplement with Folic Acid

WAIHA: Treatment

• Second Line Therapy
  • 80% patient with CR or PR with prednisone
  • 15-20% need higher than maintenance dose to stay in remission
  • <20% of patients stay in remission after withdrawal of steroids


WAIHA: Treatment

• 2nd Line Therapy
  • Splenectomy
  • Rituxan
• Other Therapies
  • Danazol
  • Cyclophosphamide
  • Cyclophosphamide
  • Mycophenolate Mofetil
  • Cyclosporine
  • Vincristine
  • Alemtuzumab
  • Ofatumumab
• Ineffective therapies
  • Azathioprine
  • BMT
  • IVIG
  • Plasma Exchange

Drug-Induced Immune Hemolysis

Three general mechanisms

- Innocent bystander
  - Quinine, Quinidine, Isoniazide
- Hapten
  - Penicillins, Cephalosporins
- True autoimmune
  - Alpha-methyldopa, L-DOPA, Procainamide

Drug-Induced Positive Antiglobulin Tests

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>DAT</th>
<th>Serum and Eluate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoantigen</td>
<td>C3 (sometimes IgG also)</td>
<td>Serum reacts with rbc only in the presence of drug; eluate non-reactive</td>
</tr>
<tr>
<td>-Drug +RBC complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Adsorption (DA)</td>
<td>IgG (sometimes C3 also)</td>
<td>React with drug-coated RBCs but not untreated RBCs- Ab to drug</td>
</tr>
<tr>
<td>-Drug binds to RBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>IgG (rarely C3 also)</td>
<td>React with normal RBCs in absence of drug</td>
</tr>
<tr>
<td>-WAIHA</td>
<td>11-36% of pts</td>
<td></td>
</tr>
</tbody>
</table>
Cold Agglutinin Disease

- Pathogenic antibodies are usually IgM
- Bind to red cells in the cooler extremities, then fix complement
- When red cells return to the warmer torso, IgM falls off
- Complement-coated red cells can be lysed directly within the vessel (intravascular hemolysis)
- Alternatively, complement-coated red cells can be engulfed by complement receptors on macrophages within the liver (extravascular hemolysis)

Cold Agglutinin Disease

- In the cold, IgM can lead to red cell agglutination
- Red cells clumps cannot pass through microvasculature, leading to cyanosis and ischemia in extremities

John Lazarchick, ASH Image Bank 2011; 2011-1053
# Cold Agglutinin Disease

## Clinical features

- Can be associated with infection with either Mycoplasma or Mononucleosis
- Can also be idiopathic or associated with a Lymphoproliferative disease
  - Most commonly IgM monoclonal gammopathy
  - Lymphoma (may only be BM involvement)

## Treatment

- Treatment is to keep patient (especially the extremities) warm. Blood and IV fluids should be warmed.
- Immunosuppression with oral chemotherapy may be required
- Steroids and splenectomy are usually ineffective.
- Rituxan (PR in 20/27 patients)
- If Rituxan refractory, can consider Eculizumab or Bortezomib
## Treatment AIHA

<table>
<thead>
<tr>
<th></th>
<th>WAIHA</th>
<th>CAD</th>
<th>Drug-IHA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Line</strong></td>
<td>Folate</td>
<td>Folate Avoid cold</td>
<td>Treat if hemolysis present</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
<td>Treat secondary cause</td>
<td></td>
</tr>
<tr>
<td><strong>2nd Line</strong></td>
<td>Splenectomy</td>
<td>Chlorambucil</td>
<td>Folate Stop drugs</td>
</tr>
<tr>
<td></td>
<td>Rituxan</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3rd Line</strong></td>
<td>Other Cytotoxic Drugs</td>
<td>Plasmapheresis?</td>
<td>Corticosteroids-severe cases</td>
</tr>
<tr>
<td>Transfusion Recommendations</td>
<td>Transfuse – least incompatible</td>
<td>Transfuse- I+, blood warmer</td>
<td>Transfuse</td>
</tr>
</tbody>
</table>

## Microangiopathic Hemolytic Anemia

- Non-immune hemolytic anemia
  - ↑reticulocytes, ↑ bili, ↑ LDH, ↓ haptoglobin
  - NEGATIVE Coomb’s
  - Prosthetic Valves, Heart valve induced, Pregnancy Associated Syndrome, HTN, Infections, Immune D/os, DIC
- Thrombotic Microangiopathy
- TTP, aHUS, HUS, Drug-Induced TMA