Evaluation of the Inpatient with Anemia

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Case 1

- 22 yo woman presents to the ED with fatigue and sob.
- Afebrile, HR 100 BP 100/60
- 10 week pregnant
- WBC 14, Hb 7, Plt count 372
Hemoglobin (Hb) 7 g/dL
Hematocrit (HCT) 26.8
Mean Corpuscular Volume (MCV) 64.1
Mean Corpuscular Hb (MCH) 17.2
Mean Corpuscular Hb Concentration (MCHC) 26.8
Red cell distribution width (RDW) 19.2
Reticulocyte count 4.89

- Hemoglobin (Hb): Oxygen carrying molecule >13.5 g/dL in men, >12 g/dL in women
- Hematocrit (HCT): Packed cell volume >41% in men, >36% in women
- Mean Corpuscular Volume (MCV): Average size of the patient's RBC 80-95 fL
- Mean Corpuscular Hb (MCH): Average Hb content per RBC 25-32 pg
- Mean Corpuscular Hb Concentration (MCHC): Average [Hb] per RBC 32-35 g/dL
- Red cell distribution width (RDW): Measure of RBC size variation (anisocytosis) 11-14%
- Reticulocyte count: % of RBC 0.8-1.5%
- Absolute retic count: Relative reticulocyte count x RBC count Normal 50,000–75,000/µL
A few considerations

• Hb, HCT and RBC are affected by volume status
  • Active bleeding
  • Pregnancy
• Normal ranges may not apply to some individuals
  • Athletes
  • People living in high altitude
  • Smokers
  • African-Americans

Anemia

Low/normal reticulocyte count
  • Decreased production
    • Nutritional deficits
    • Bone marrow pathology

High reticulocyte count
  • Increased loss/destruction
    • Blood loss
    • Hemolysis
Normal Red Cell Production (Erythropoiesis)

Kidney

Blood vessel

Normal Red Cell Production (Erythropoiesis)

Kidney

Blood vessel

Bone marrow

Pluripotent stem cell

Erythroid stem cell

3-4 days
Normal Red Cell Production (Erythropoiesis)

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 deficiency anemia

- Public health problem – huge variation around the world
- Affects most commonly children aged 0-5 years, women of childbearing age and pregnant women
- Major cause of disability globally

Causes of Iron Deficiency Anemia

- Increased iron requirements
  - Blood loss
  - Pregnancy and lactation
- Inadequate supplies
  - Insufficient dietary iron
  - Impaired absorption
### Iron Intake

- **Recommended dietary iron:**
  - Ages 9-13: 8 mg
  - Ages 14-18: 11 mg for boys and 15 mg for girls
  - > 19: 8 mg for men, 18 mg for women (until age 50)
  - Pregnant women: 30 mg

- Main source of iron intake is **meat (especially red meat)**

### Iron metabolism

- 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
  - Hb: 2g
  - Iron containing proteins: 400 mg
  - Iron in plasma bound to transferrin: 3-7 mg
  - Storage iron (ferritin or hemosiderin): 0.5 g in women and 1 g in men
Diagnosis: Symptoms

- **Pica (25%)**: Compulsive ingestion of a non-food substance such as starch, clay, ground, ice
- **Beeturia (49-80%)**: urine turns red after ingestion of beets
- **Restless legs syndrome (10%)**: Urge to move the legs usually accompanied by uncomfortable sensations that begins or worsens during periods of rest and relieved by movement. Worse in the evening/night

Diagnosis: Laboratory

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>IDA</th>
<th>ACD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Measures circulating iron bound to transferrin. NOT a marker of iron status (will change with even just one meal)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Transferrin (TIBC)</td>
<td>Circulating transport protein for iron</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Serum iron $\div$ TIBC x 100</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Circulating iron storage protein, acute phase reactant. Best value for iron deficiency</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade (brand) name</th>
<th>Concentration of elemental iron</th>
<th>Dosing (adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric carboxymaltose (FCM)</td>
<td>Injectafer, Ferinject</td>
<td>50 mg/mL</td>
<td>Two doses, given seven or more days apart</td>
</tr>
<tr>
<td>Ferric gluconate (FG)</td>
<td>Ferrlecit</td>
<td>12.5 mg/mL</td>
<td>Multiple doses</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>Feraheme</td>
<td>30 mg/mL</td>
<td>Single dose or two doses given 3-8 days apart</td>
</tr>
<tr>
<td>Iron dextran, low molecular weight (LMW ID)</td>
<td>INFeD, CosmoFer</td>
<td>50 mg/mL</td>
<td>Multiple doses or one single dose</td>
</tr>
<tr>
<td>Iron isomaltoside</td>
<td>Monofer</td>
<td>100 mg/mL</td>
<td>Single dose or up to three doses given over seven days</td>
</tr>
<tr>
<td>Iron sucrose (IS)</td>
<td>Venofer</td>
<td>20 mg/mL</td>
<td>Multiple doses</td>
</tr>
</tbody>
</table>
Anemia of Inflammation

- Decreased RBC production + decreased RBC survival
- Reduced iron absorption in the GI tract and trapping of iron in macrophages
- Relative decrease in EPO production
- Decrease bone marrow response to EPO mediated by inflammatory cytokines

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%)
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
- If intake stops, takes 2-3 years for storage to be depleted
- Requires IF produced by gastric cells for absorption in ileum

**Folate**
- Sources: green leafy vegetables
- Daily requirement about 50-100 ug/day
- Reserves last 3-4 months
- Absorbed in jejunum and ileum
<table>
<thead>
<tr>
<th>Signs/Symptoms of B12 Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anemia, hypersegmented neutrophils</td>
</tr>
<tr>
<td>• “Beefy Red” tongue, smooth surface of the tongue</td>
</tr>
<tr>
<td>• Neurologic</td>
</tr>
<tr>
<td>• demyelination of the posterior and lateral columns of the spinal cord</td>
</tr>
<tr>
<td>• paresthesia, loss of position/vibratory sense</td>
</tr>
<tr>
<td>• in advanced disease, neuropathy, muscle weakness, and even CNS symptoms (irritability, somnolence, psychosis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis and Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Check MMA with borderline levels of Vit B12 and treat if elevated</td>
</tr>
<tr>
<td>• Folate deficiency: 1-5mg daily of oral folic acid</td>
</tr>
<tr>
<td>• Vit B12 deficiency:</td>
</tr>
<tr>
<td>• IV: 1000 mcg once per week until the deficiency is corrected and then once per month</td>
</tr>
<tr>
<td>• Oral: 1000 to 2000 mcg daily</td>
</tr>
</tbody>
</table>
Miscellaneous: 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


Case 2

- 43 yo man with no remarkable PMhx that presents to the ED with fatigue
- PE: hepatosplenomegaly and jaundice
- Hb 7, WBC 5, plt count 200K
- MCV 100
- Retic count 5%
Anemia with high reticulocyte count

- Normal/High MCV
  - Acute hemorrhage
  - Hemolytic Anemia
    - Autoimmune
    - Microangiopathic Hemolytic Anemia
    - Hemoglobinopathies
    - Membranopathies/enzymopathies
- Low MCV (microcytosis)
  - Hemoglobinopathies

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
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**

**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
# Warm-Antibody Hemolytic Anemias

## Treatment

- Transfuse only if the patient is severely symptomatic
- 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
  - 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
  - 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-methylldopa, 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 - Drug + RBC complex</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 Adsorption (DA) - Drug binds to RBC</td>
<td>IgG (sometimes C3 also)</td>
<td>React with drug-coated RBCs but not untreated RBCs- Ab to drug</td>
</tr>
<tr>
<td>Autoantibodies - WAIHA</td>
<td>IgG (rarely C3 also)</td>
<td>React with normal RBCs in absence of drug</td>
</tr>
<tr>
<td>11-36% of pts</td>
<td></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)
Cold Agglutinin Disease 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.
- Rituximab (PR in 20/27 patients)
- If Rituximab Refractory, can consider Eculizumab or Bortezomib

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

Structural abnormalities of Hb

- Thalassemia
- Sickle Cell disease
- G6PD deficiency
- Hereditary Spherocytosis
**Alpha-thalassemia**

- **αα/αα**: Normal
- **-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
  - No clinical disease
- **|--/αα**: 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
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 (Sickle Cell Anemia)</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>$\beta^s-\beta^+\text{thal}$</td>
<td>7</td>
</tr>
<tr>
<td>Heterozygous S-$\beta^-$ thal</td>
<td>$\beta^s-\beta^-\text{thal}$</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
Complications of SCD


Evaluation of inpatient with anemia

Patient history: acuity, prior medical history, family history and associated symptoms
Physical exam: hepato/splenomegaly, LNP, associated infection
Lab: MCV, MCH, retic count, peripheral smear
<table>
<thead>
<tr>
<th>Red blood cell transfusions in hospitalized patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &lt; 8 g/dL</td>
</tr>
<tr>
<td>• Preexisting CAD</td>
</tr>
<tr>
<td>• ACS (8-10 g/dL)</td>
</tr>
<tr>
<td>• Cardiac surgery</td>
</tr>
<tr>
<td>• &lt; 7 g/dL</td>
</tr>
<tr>
<td>• Non cardiac surgery</td>
</tr>
<tr>
<td>• Intensive care unit</td>
</tr>
<tr>
<td>• GIB</td>
</tr>
</tbody>
</table>