Approach to Anemia

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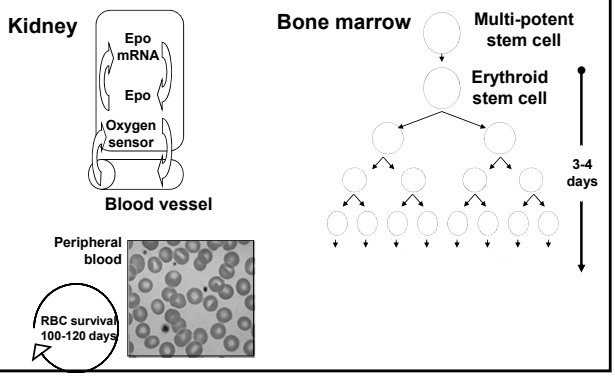
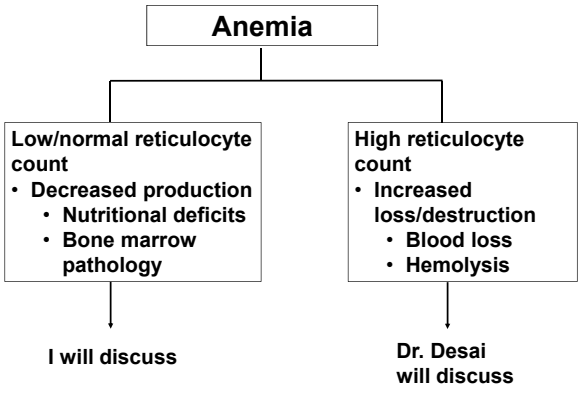
Normal Red Cell Production (Erythropoiesis)



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)



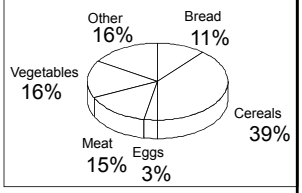
Anemia with low/normal reticulocyte count

- 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



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

Andrews, NC. N Engl J Med 1999;341:1986-1995

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

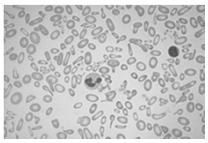
- Inadequate iron supply
  - Insufficient dietary iron
  - Impaired iron absorption
    - Gastric (bariatric) surgery
    - Atrophic gastritis
    - Intestinal malabsorption
    - Celiac disease
    - *H. pylori* infection

Neurologic syndromes associated with iron deficiency

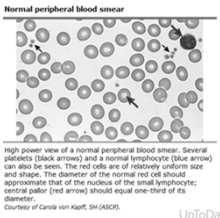
- **Pica**
  - Latin word for *magpie*, a bird which is reputed to eat almost anything
  - Definition: Compulsive ingestion of a non-food substance such as starch, clay, earth, ice
  - Ceases within days of therapy
  - Occurs in ~25% of patients with iron deficiency anemia from any cause
  - More commonly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



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 <7days; 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

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

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
  - *INFeD®*
  - *Dexferrum®*
- Sodium ferric gluconate complex (SFGC)
  - *Ferrlecit®*
- Iron Sucrose
  - *Venofer®*
- Ferumoxytol
  - *Feraheme™*

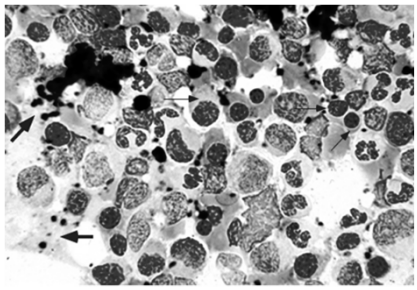
Anemia of Chronic Disease

- Characteristics
  - Immune-driven by inflammatory cytokines
  - Diversion of iron into RE system (iron not in the "right place"
  - Blunted erythropoietin response
- Diagnosis- iron status

Parameter	Anemia of Chronic Disease	Iron deficiency anemia
Serum Iron	Reduced	Reduced
TIBC	Reduced-Normal	Increased
% saturation (TSAT)	Reduced	Reduced
Ferritin	Normal-increased	Reduced
sTfR	Normal	Increased
Cytokine levels	Increased	Normal

Anemia of Chronic Disease

- Impaired iron transfer from reticuloendothelial macrophages and duodenum to plasma transferrin, then to liver



http://www.uptodate.com/contents/causes-and-diagnosis-of-iron-deficiency-anemia-in-the-adult?topicKey=HEME%2F7150&elapsedTimeMs=0&view=print&displayedView=full

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 erythropoesis
  - Intramedullary hemolysis
  - Decreased red cell survival/misshapen cells

Vitamin B12 and folate

Vitamin B12

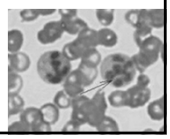
- Sources: dietary meat products
- Daily requirement 2-5 ug/day
- Total body stores 2-4 mg
- If intake stops, takes 2-3 years for storage to be depleted

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 jejenum and ileum

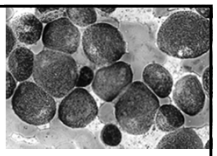
Signs/Symptoms of B12 Deficiency

- 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)



Wikipedia, https://en.wikipedia.org/wiki/Hypersegmented_neutrophil

Bone marrow process



- Broad DDx, including
  - Acute or chronic leukemia
  - Myelodysplatic 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:

αα/αα — Normal

-α/αα — Silent carrier
SE Asia, 28% African Americans.
Normal or slightly ↓MCV; ± HbH inclusions

-α/-α, --/αα — α-thalassemia minor
SE Asia, 3% of Black Americans, Mediterranean
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

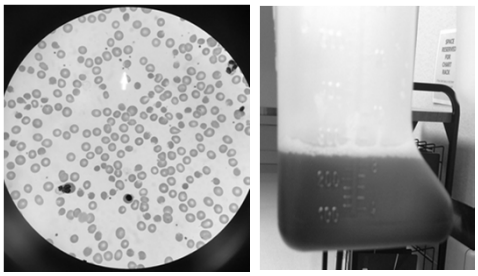
- Low MCV (microcytosis)
  - Hemoglobinopathies (such as some sickle cell)
- Normal/High MCV
  - Acute hemorrhage
  - Hemolytic Anemia
    - Hemoglobinopathies
    - Membranopathies/enzymopathies
    - Autoimmune
    - Microangiopathic Hemolytic Anemia

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 α and β chains
  - Alter the shape or structure of the globin molecule

Unstable Hemoglobins

- Denaturation and precipitation of globin chains in RBC's → Heinz bodies which cling to membrane → removed in spleen → hemolysis



The Common Variants of Sickle Cell Disease

Name	Genotype	Percent
Homozygous SS (*Sickle Cell Anemia*)	β^S-β^S	65
Heterozygous SC	β^S- β^C	24
Heterozygous S-β^+ thal	β^S- β^+ thal	7
Heterozygous S-β° thal	β^S- β° thal	3

Sickle Cell Anemia Pathophysiology

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

Owusu-Ansah 2015

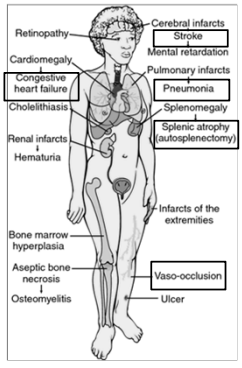
Mortality in Sickle Cell Disease

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**

Diggs LM. Anatomic lesions in sickle cell disease. Sickle cell disease: diagnosis, management, education, and research. St. Louis: C.V. Mosby, 1973:189-229
Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Pediatrics 1989;84:500-508
Platt et al. Mortality In Sickle Cell Disease – Life Expectancy and Risk Factors for Early Death. N Engl J Med 1994; 330:1639-1644
Quinn C T et al. Survival of Children with Sickle Cell Disease. Blood 2004;103:4023-4027

Complications of SCD



- **Sepsis**
- **Priapism**
- **Myocardial Infarction**
- **Multiorgan Failure**
- **Transfusion Reaction**

Konotey-Ahulu FID. The Sickle Cell Disease. Clinical Manifestations Including the "Sickle Crisis". *Arch Intern Med.* 1974;133(4):611-619.

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

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 methlyprednisolone IV
  - Continue until Hb > 10g/dL then taper
  - Continue with Vitamin D, Ca, + bisphosphonates
  - Consider PCP prophylaxis
  - Supplement with Folic Acid

Lechner et al. How I Treat Autoimmne Hemolytic Anemia. Blood 2010.
Crowther et al. Evidence-based focused review of the treatment of idiopathic warm immune hemolytic anemia in adults. Blood 2011

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

Lechner et al. How I Treat Autoimmne Hemolytic Anemia. Blood 2010.
Crowther et al. Evidence-based focused review of the treatment of idiopathic warm immune hemolytic anemia in adults. Blood 2011

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

Lechner et al. How I Treat Autoimmne Hemolytic Anemia. Blood 2010.
Crowther et al. Evidence-based focused review of the treatment of idiopathic warm immune hemolytic anemia in adults. Blood 2011

Drug-Induced Immune Hemolysis
Three general mechanisms

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

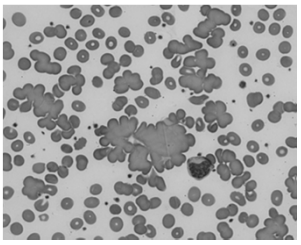
Drug-Induced Positive Antiglobulin Tests

Mechanism	DAT	Serum and Eluate
Neoantigen -Drug +RBC complex	C3 (sometimes IgG also)	Serum reacts with rbcs only in the presence of drug; eluate non-reactive
Drug Adsorption (DA) -Drug binds to RBC	IgG (sometimes C3 also)	React with drug-coated RBCs but not untreated RBCs- Ab to drug
Autoantibodies -WAIHA	IgG (rarely C3 also) 11-36% of pts	React with normal RBCs in absence of drug

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 DiseaseTreatment

- **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

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

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**