Evaluation of the Inpatient with Anemia

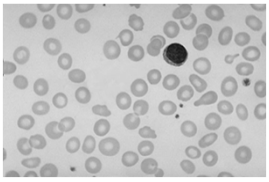
Camila Masias, M.D.
Assistant Professor
Division of Hematology
The Ohio State University Wexner Medical Center

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**

More details…

- **Hb 7 g/dL**
- **HCT 26.8**
- **MCV 64.1**
- **MCH 17.2**
- **MCHC 26.8**
- **RDW 19.2**
- **Retic count 4.89**



Hemoglobin	Oxygen carrying molecule	>13.5 g/dL in men, > 12 g/dL in women
Hematocrit	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

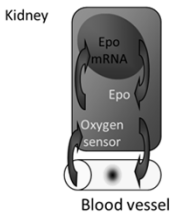
- Hb, HCT and RBC are affected by volume status
  - Active bleeding
  - Pregnancy
- Normal ranges may not apply to some individuals
  - Athletes
  - People living in high altitude
  - Smokers
  - African-Americans

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)



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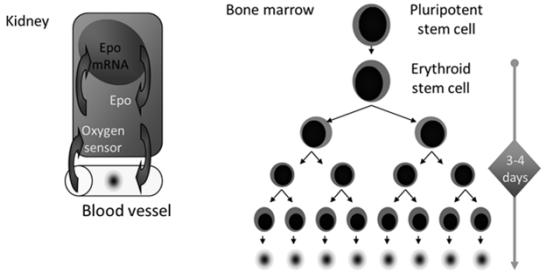

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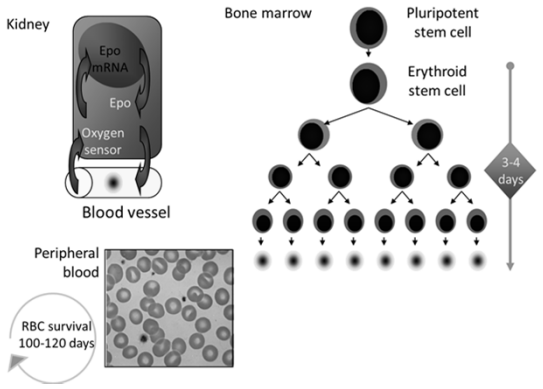


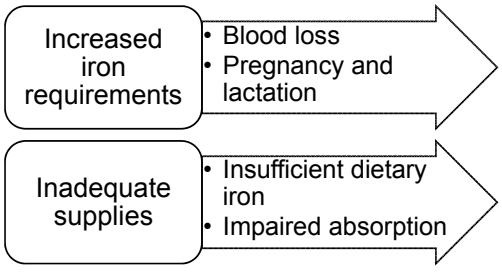
Anemia with low/normal reticulocyte count

- **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



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

Test		IDA	ACD
Iron	Measures circulating iron bound to transferrin. NOT a marker of iron status (will change with even just one meal)	↓	↓
Transferrin (TIBC)	Circulating transport protein for iron	↑	↓
Transferrin saturation	Serum iron ÷ TIBC x 100	↓↓	↓
Ferritin	Circulating iron storage protein, acute phase reactant. Best value for iron deficiency	↓	↑

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

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

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

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)

Diagnosis and Treatment

- Check MMA with borderline levels of Vit B12 and treat if elevated
- Folate deficiency: 1-5mg daily of oral folic acid
- Vit B12 deficiency:
  - IV: 1000 mcg once per week until the deficiency is corrected and then once per month
  - Oral: 1000 to 2000 mcg daily

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

http://www.pathpedia.com/education/eatlas/histopathology/bone_marrow/acute_lymphoblastic_leukemia_b-cell_(b-all).aspx

Case 2

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

Anemia with high reticulocyte count

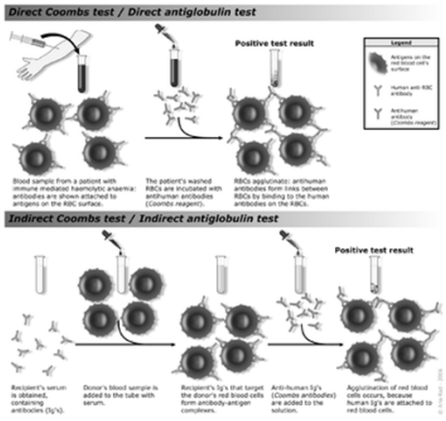
- Normal/High MCV
  - Acute hemorrhage
  - Hemolytic Anemia
    - Autoimmune
    - Microangiopathic Hemolytic Anemia
    - Hemoglobinopathies
    - Membranopathies/enzymopathies
- Low MCV (microcytosis)
  - Hemoglobinopathies

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

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

- Transfuse only if the patient is severely symptomatic
- 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
  - 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

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WAIHA: Treatment

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

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Drug-Induced Immune Hemolysis
Three general mechanisms

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

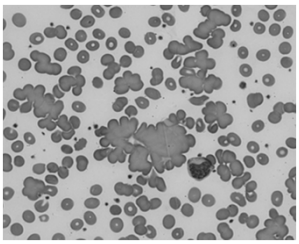
Drug-Induced Positive Antiglobulin Tests

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 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 <u>usually ineffective.</u>
- Rituximab (PR in 20/27 patients)
- If Rituximab 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

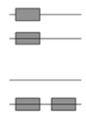
Structural abnormalities of Hb

- 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

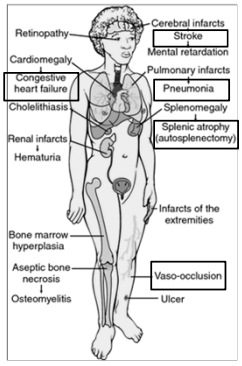
Name	Genotype	Percent
Homozygous SS (*Sickle Cell Anemia*)	β^S-β^S	65
Heterozygous SC	β^S- β^C	24
Heterozygous S-β^+ thal	β^S- β^+ thal	7
Heterozygous S-β° thal	β^S- β° thal	3

Sickle Cell Anemia Pathophysiology

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

Owusu-Ansah 2015

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.

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

Red blood cell transfusions in hospitalized patients

- < 8 g/dL
  - Preexisting CAD
  - ACS (8-10 g/dL)
  - Cardiac surgery
- < 7 g/dL
  - Non cardiac surgery
  - Intensive care unit
  - GIB