Evaluation of the Inpatient with Anemia

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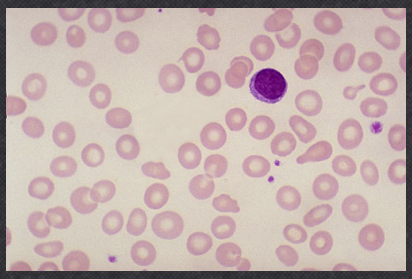
Case 1

- 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

More details…

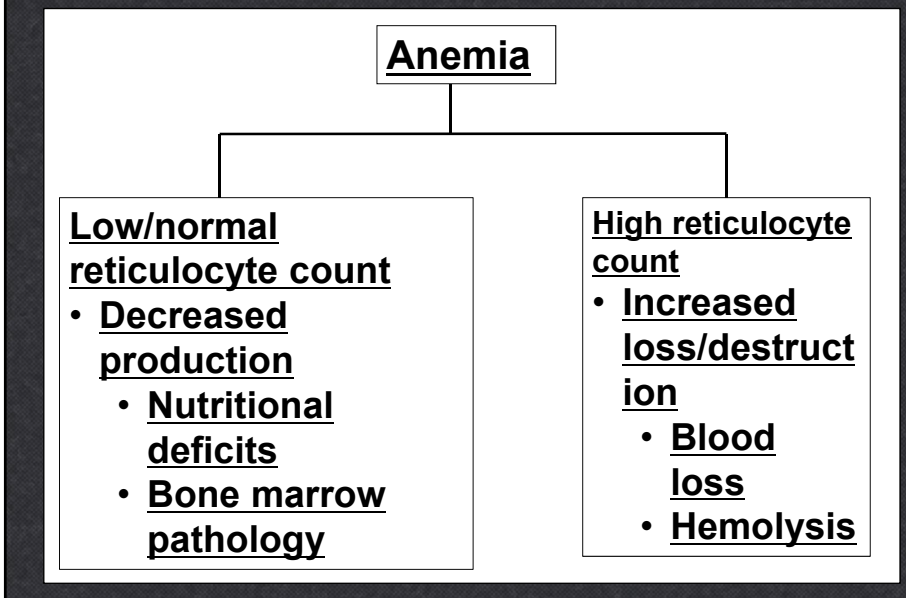
- Hb 7 g/dL
- HCT 26.8
- MCV 64.1
- MCH 17.2
- MCHC 26.8
- RDW 19.2
- Retic count 4.89



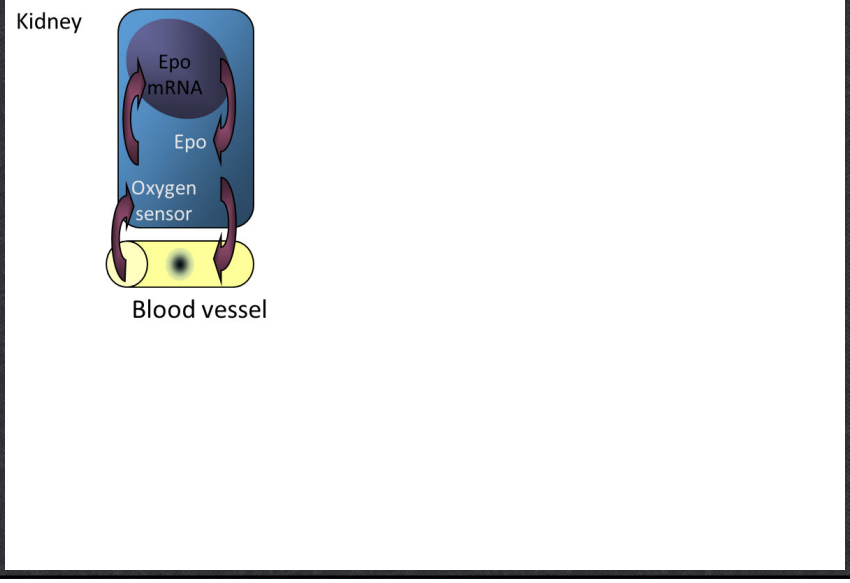
Hemoglobin	Oxygen carrying molecule	>13.5 g/dL in men, > 12 g/dL in women
Hematocrit	Packed cell volume	>41% in men, >36% in women
Mean Corpuscular Volume (MCV)	Average size of the patient's RBC	80-95 fL
Mean Corpuscular Hb (MCH)	Average Hb content per RBC	25-32 pg
Mean Corpuscular Hb Concentration (MCHC)	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



Normal Red Cell Production (Erythropoiesis)



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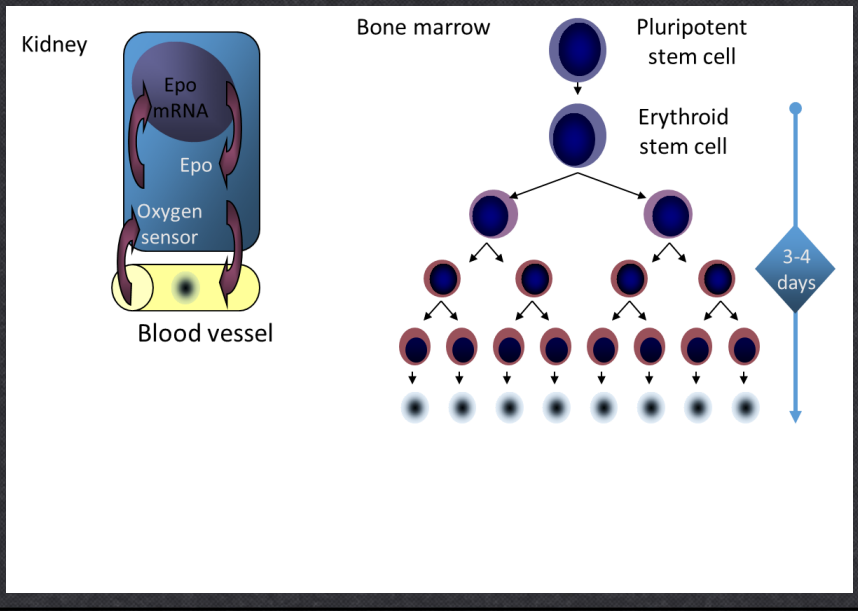

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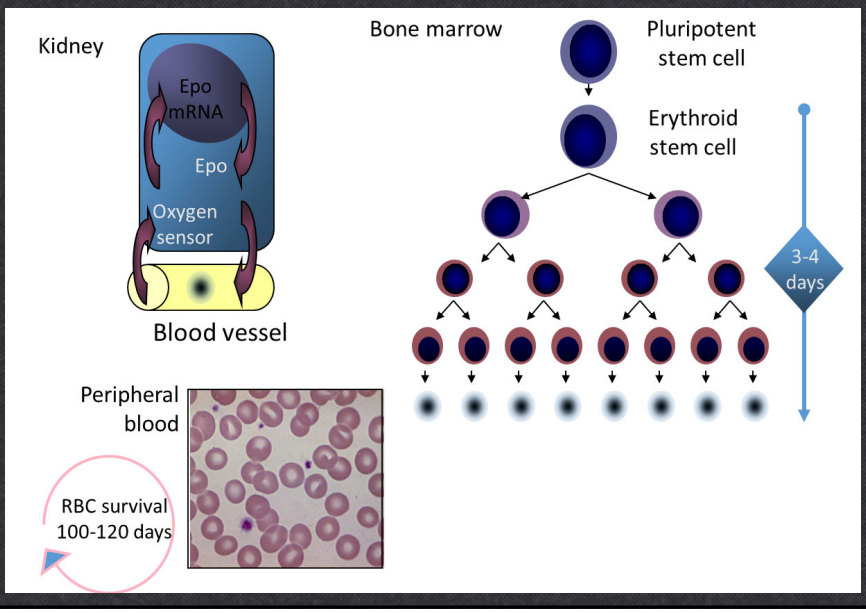


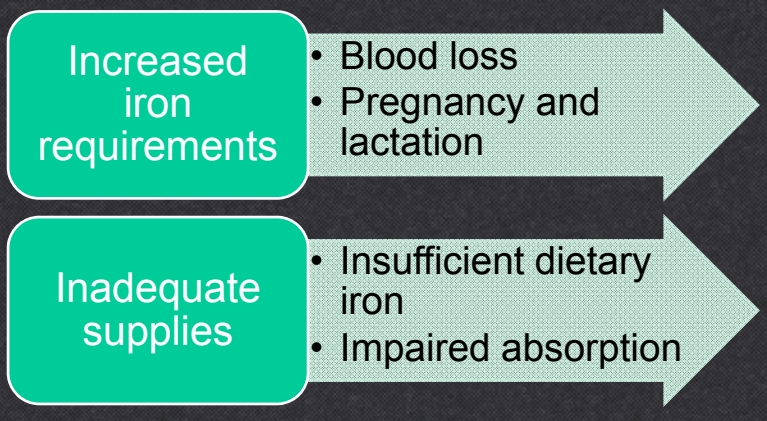
Anemia with low/normal reticulocyte count

- 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

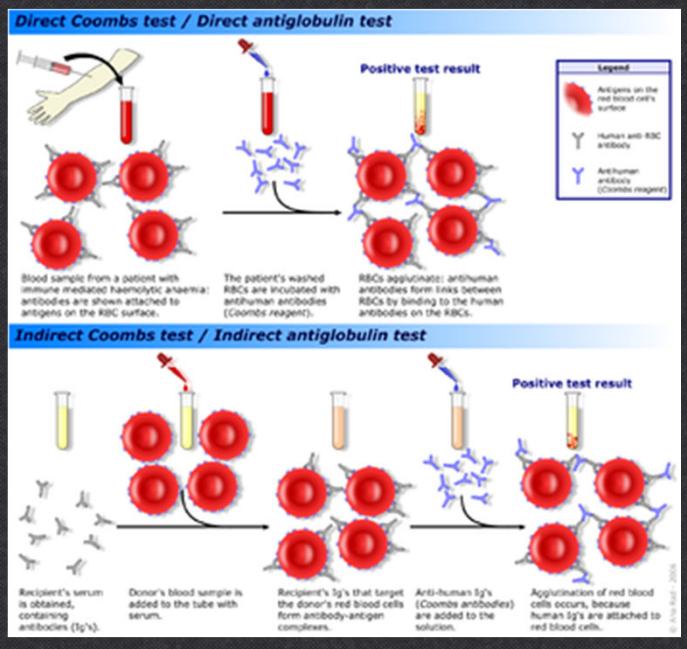
- Normal/High MCV
  - Acute hemorrhage
  - Hemolytic Anemia
    - Autoimmune
    - Microangiopathic Hemolytic Anemia
    - Hemoglobinopathies
    - Membranopathies/enzymopathies
- Low MCV (microcytosis)
  - Hemoglobinopathies

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

Lechner et al. How I Treat Autoimmne Hemolytic Anemia. Blood 2010.
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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

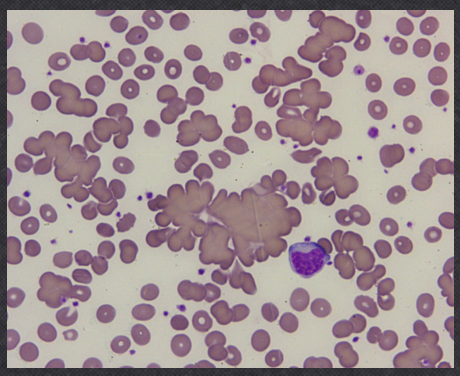
Drug-Induced Positive Antiglobulin Tests

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 usually ineffective.
- 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

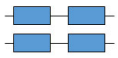
Microangiopathic Hemolytic Anemia

- 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

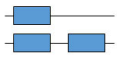
Structural abnormalities of Hb

- Thalassemia
- Sickle Cell disease
- G6PD deficiency
- Hereditary Spherocytosis

Alpha-thalassemia



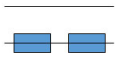
αα/αα — **Normal**



-α/αα — **Silent carrier**

SE Asia, 28% African Americans.
Normal or slightly ↓MCV; ± HbH inclusions

-α/-α



--/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

The Common Variants of Sickle Cell Disease

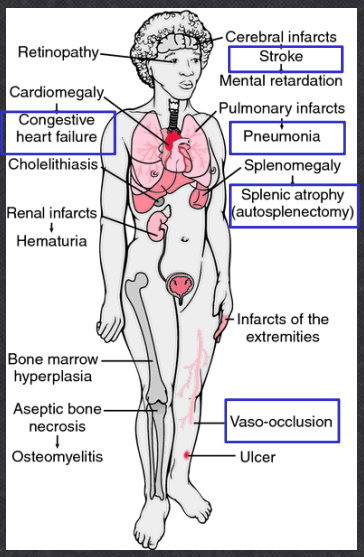
Name	Genotype	Percent
Homozygous SS (*Sickle Cell Anemia*)	β^S-β^S	65
Heterozygous SC	β^S- β^C	24
Heterozygous S-β^+ thal	β^S- β^+ thal	7
Heterozygous S-β° thal	β^S- β° thal	3

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