Anemia in Women

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What is blood?

- Plasma (60%)
  - Water
  - Dissolved ions and protein
- Cellular components (40%)
  - WBCs
  - RBCs
  - Platelets

Erythrocyte Development

1. Stem cell
2. Early RBC progenitor
3. Late RBC progenitor
4. Pronormoblast
5. Basophilic normoblast
6. Polychromatophil
7. Orthochromatic normoblast
8. Reticulocyte (large cell)
9. Mature RBC

What are reticulocytes?

- Adolescent RBCs
  1. Erythropoietin from kidneys
  2. Bone marrow responds
  3. Reticulocytes are produced
  4. Released into circulation

Accelerated RBC production ⇒ **more reticulocytes!**

What accelerates RBC production?

1. Hemolysis
2. Blood loss
3. Hemoglobin S disease
4. Cancer
5. Pregnancy
6. Iron replacement in iron deficiency anemia

What if reticulocytes are decreased?

- Normal
  - 1-2% of RBCs are reticulocytes
- Decreased when bone marrow is not making RBCs
  - Iron deficiency
  - Aplastic anemia
  - Chronic infection
  - Untreated pernicious anemia

What is hemoglobin?

- Oxygen carrying protein
- 2 pairs of polypeptide chains (globins)
  - 2 alpha chains
  - 2 beta chains
- Each chain has heme molecule
  - Heme = iron + protoporphyrin
- Hemoglobinopathy
  - Abnormal hemoglobin

Types of Hemoglobin (Hb)

Fetal hemoglobin
- Hb F

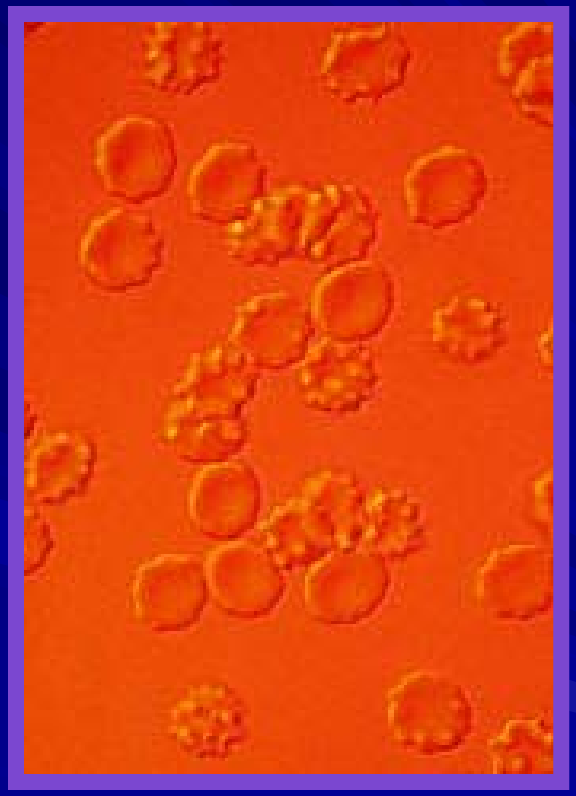
- Hb A
  - Adult hemoglobin
  - 2 alpha and 2 beta chains
- Hb A_{1c}
  - Hb A with glucose
  - 3-6 % normal
  - Elevated with diabetes

Hemoglobinopathy

- Sickle cell
  - Hb S – beta chain mutation
  - Most common hemoglobinopathy
- Thalassemia
  - Deletion or mutation of chain

Red Blood Cell Indices

- RBC
- Hgb
- Hct
- MCV
- MCH
- MCHC
- RDW
- Reticulocytes



Red Blood Cell Count (RBC)

- Number of RBCs/cubic ml
- 3.6-5.0 x 10U/ml
- Lower in recumbent position
- Exercise/excitement increase
- Dehydration increases

Hemoglobin (Hb)

- Amount of hemoglobin in blood
- 30% of RBC is Hb
- 12-16 g/dL

Hematocrit (Hct)

- Volume of RBCs
- Immediate acute loss
  - Equilibrium occurs
  - HCT will not reflect blood loss
- 37-47% by venipuncture
- 42-44% by finger stick

Mean Corpuscular Volume (MCV)

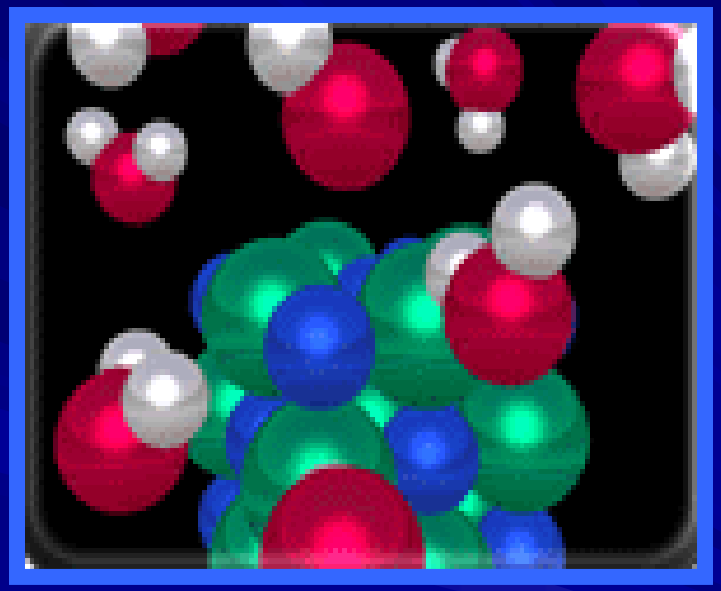
- Average volume of single RBC
- Classifies anemia
  - Microcytic
  - Normocytic
  - Macrocytic
- 80-100 (107) fl/L
- 80-83 low normal

Mean Corpuscular Hemoglobin (MCH)

- Average weight for each RBC
- Picograms
- 26-34 pg
- Not used as much as others

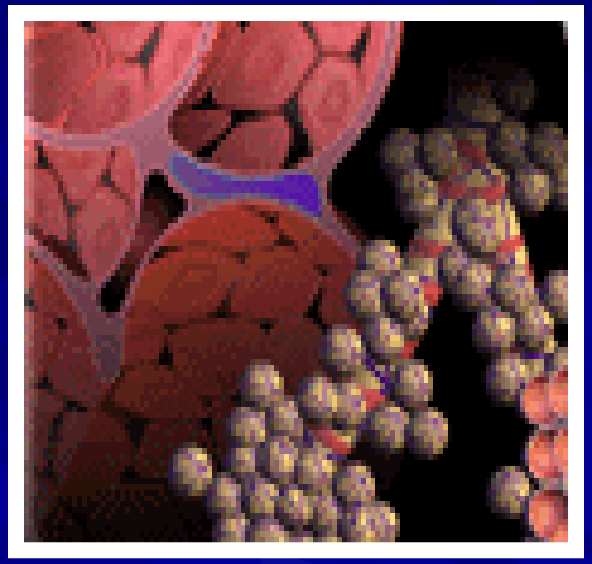
Mean Corpuscular Hemoglobin Concentration (MCHC)

- Average hemoglobin concentration
- 31 g/- 37 dL



Red Cell Distribution Width (RDW)

- Coefficient of variation of red cells
- Anisocytosis
  - Variation in cell size
- Normal 11.5-14.5



Reticulocytes

- Number of immature RBCs
- May increase MCV (large cells)

Other RBC Indices

- Serum Ferritin
- Serum Iron
- Total Iron Binding Capacity
- Transferrin Saturation
- Serum Folate
- Serum Vitamin B-12

Serum Ferritin
Body's Storage of Iron

- Low serum ferritin
  - Iron deficiency
  - First abnormal indice with iron deficiency
- Normal serum ferritin
  - Chronic disease
- Increased serum ferritin
  - Iron overload
  - Inflammatory diseases
  - Alcoholism

Iron Indices

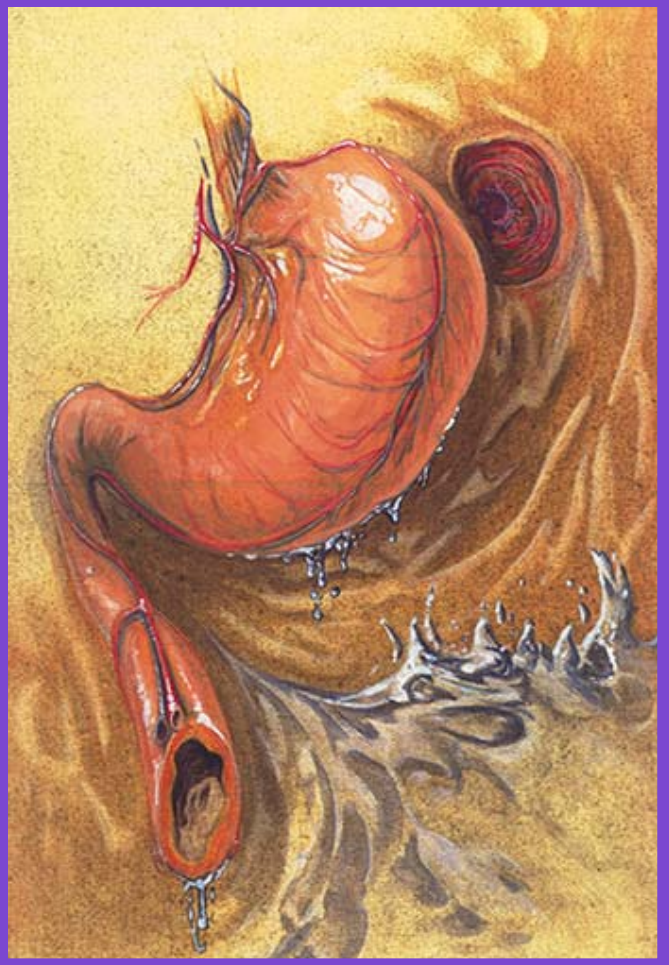
- Transferrin
  - Protein that transports iron
  - Measured by total iron binding capacity (TIBC)
- Serum Iron
  - Amount of iron bound to transferrin
- Transferrin saturation
  - Percentage of serum iron to TIBC
  - 20-50%

Red Blood Cell Folate

- Diagnose macrocytic anemia
- Low folate
  - Folate deficiency
  - Must be low for > 20 weeks to change cells
  - Pancytopenia ?
- Low RBC folate
  - Specific for folic acid deficiency

Serum B-12

- Low B-12
- Diagnose macrocytic anemia



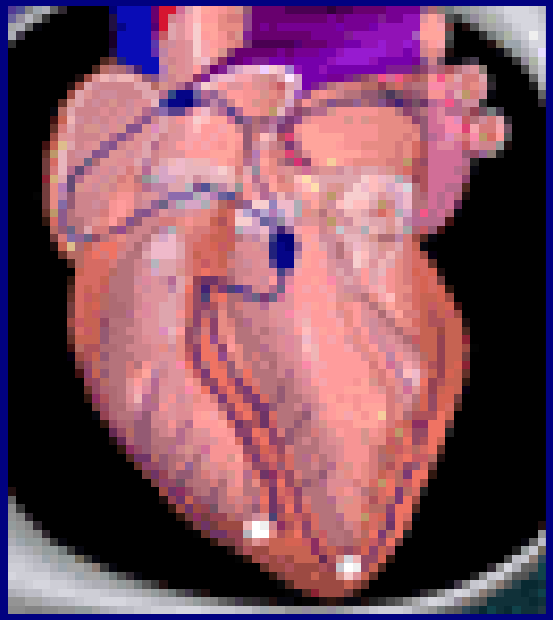
Classification of Anemia by Etiology

- Decreased healthy RBC production
  - Bone marrow does not produce enough cells
  - Maturational defect in cells

Classification of Anemia by Etiology

- Increased RBC loss
  - Blood loss
- RBC destruction
  - Intrinsic (sickle cell)
  - Extrinsic (mechanical cardiac valve)

  Combination of above



Classification by RBC Morphology

- Size
  - Microcytic: decreased MCV
  - Normocytic: normal MCV
  - Macrocytic: increased MCV
- Color
  - Normochromic
  - Hypochromic

Microcytic Anemias

- Iron deficiency
- Thalassemia
- Anemia of chronic disease

Macrocytic Anemias

- Megaloblastic
  - Vitamin B-12 deficiency
  - Folate deficiency
- Non megaloblastic
  - Chemotherapy
  - Liver disease
  - Reticulocytosis – excess of immature cells
  - Myxedema - chronic hypothyroidism

Normocytic Anemias

- Acute blood loss
- Anemia of chronic disease
- Infection
- Medications

Signs and Symptoms of Anemia

- Often asymptomatic
- Systolic murmur
- Hypotension
- Glossitis
- Chilitis

Signs and Symptoms of Anemia

- Dry skin
- Thin hair
- Pallor
- Nail ridges
- Pale conjunctiva

Microcytic Anemia
Iron Deficiency Anemia

Most common anemia

Normal Iron Metabolism

- Ferritin: stored iron
  - 30% of total body iron
  - Found in liver,spleen, and bone marrow
- Transferrin
  - Transfers iron from storage to functional pool

Normal Iron Metabolism

- Transferrin recognized by target tissues via a specific receptor
- Cells with greater iron need express greater number of receptors
- Iron internalized by endocytosis

Normal Iron Metabolism

- Apoferritin traps iron as part of storage complex (ferritin)
- Erythropoietin secreted by kidneys
  - Stimulates RBC production

Lab Findings

	B12	Folate	Iron	Chronic Disease
Hgb	↓	↓	↓	↓
Hct	↓	↓	↓	↓
MCV	↑	↑	↓	↓/→
MCH	↑	↑	↓	↓/→
MCHC	→	→	↓	↓/→
Size	macrocytic	macrocytic	microcytic	normocytic

Lab Values

- Smear
  - Hypochromic
  - Microcytic
  - Anisocytosis
    - Ani – Greek for unequal
    - Abnormal sizes of RBCs
  - Poikilocytosis
    - Poikolo – Greek for irregular
    - Abnormal shapes of RBCs

Lab Values

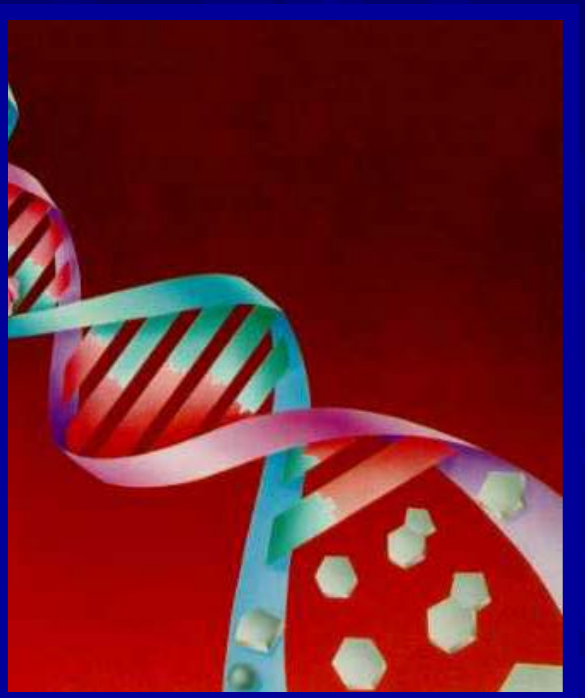
- Serum ferritin
  - <15 mcg/L
- TIBC
  - Rises
- Serum iron
  - <30 mcg/dL
- MCV
  - <80
- MCHC
  - <30
- RDW
  - Elevated

Evaluation of Iron Status

- Serum Ferritin
  - Indicates total body iron stores
  - < 15 mcg/L deficiency
  - Increase
    - Systemic inflammation
    - Infection
    - Liver disease

Evaluation of Iron Status

- Transferrin Saturation
  - (Serum iron)/ total iron binding capacity (TIBC)
  - Saturation < 20% indicates deficiency



Signs and Symptoms

- Fatigue
- Tachycardia
- Shortness of breath
- Left ventricular hypertrophy
- Angina

Iron Deficiency Anemia

30% of Diagnosed Anemia

- Inadequate intake
- Malabsorption
- Excessive blood loss
  - Menstrual
  - GI
- Increased requirements
  - Pregnancy or lactation

Differential Diagnosis

- Anemia of chronic disease
  - Normal or elevated ferritin
- Thalassemia
  - More microcytosis
  - Normal iron parameters
- Iron deficiency responds to iron therapy

Oral Iron Therapy

- Iron dose (adults)
  - Recommended dose = 200mg/day
  - Duration = 3 months
  - Will respond in 10 - 21 days
- Ferrous sulfate preferred
  - Adverse effects
    - GI complaints

Comparison of Oral Products

Product	% Iron	Daily dose	Fe/day
Ferrous sulfate	20%	325mg tid	195mg
Ferrous fumarate	33%	200mg tid	198mg
Ferrous gluconate	11%	600mg tid	198mg

Administration of Oral Iron

- Empty stomach if no GI distress
- Administer with meat, fish, or Vitamin C foods
- Keep out of reach of children

Parenteral Iron Therapy (Iron Dextran)

- Noncompliance or malabsorption
- Single dose IV
  - Dose: 500-3000 mg
  - Iron content = 50mg/ml
  - Total mg Iron=[0.0442 x (desired Hgb-Obs Hgb) x IBW + (0.26 x IBW)] x 50

Iron-Rich Foods

- Animal protein
  - Heme iron
- Deep green vegetables
- Iron-fortified cereals

Parenteral Iron Therapy (Iron Dextran)

- Side effects - anaphylaxis
  - Arthralgia
  - Myalgia
  - Flushing
  - Malaise
  - Fever
  - Allergy/anaphylaxis
- Give test dose: 25mg (0.5ml)

Follow-Up

- Repeat CBC 2-4 weeks after therapy initiated
- If no response
  - Evaluate for other anemia

Anemia of Chronic Disease

- Microcytic anemia
- Normocytic/normochromic anemia
- 25% of all diagnosed anemia

Chronic Diseases Causing Anemia

- Chronic infection or inflammation
- HIV
- Cancer/malignancy
- Liver failure
- Chronic renal failure
  - Decreased erythropoietin

Clinical Findings

- Signs and symptoms of anemia
- Labs
  1. Low serum iron
  2. Low TIBC
  3. Normal or increased serum ferritin
- Dialysis
  1. Low folate
- GI blood loss
  1. Positive guaiac

Further Lab Findings

1. Hct rarely below 25%
   (Except with renal failure)
2. MCV normal or slightly low
3. RBC morphology normal
4. Reticulocytes normal/low
5. Serum ferritin normal/low
6. Serum iron low
7. Transferrin saturation very low

Common Features

- Hypo-proliferative bone marrow
- Low serum erythropoietin

Goals of Therapy

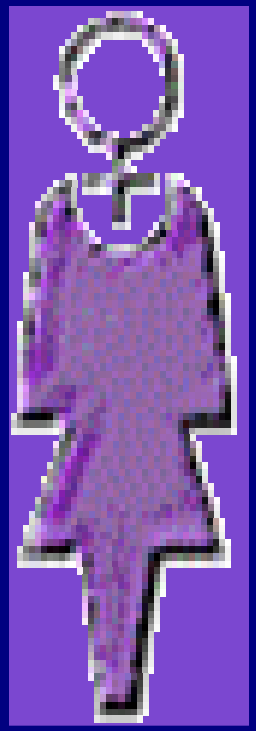
- Increase Hct to target 30% to 36%
- Decrease morbidity and mortality
- Decrease transfusion requirements

Erythropoietin

- 50-100U/kg TIW, IV or SC
- Reduce dose when:
  1. HCT approaches 36%
  2. HCT increases > 4 points in 2 weeks
- Increase dose when:
  1. Hct does not increase > 5-6 points after 8 weeks
  2. Hct is below target

Side Effects

- Hypertension (25%)
- Arthralgia
- Nausea



Factors Decreasing Response to Therapy

- Iron deficiency
- Blood loss
- Infection

Iron Supplementation with Erythropoietin

- May be PO or IV
  - PO: 200mg elemental iron daily
  - IV: 100mg for 10 consecutive treatments
- Avoid enteric-coated formulations

Lead Poisoning

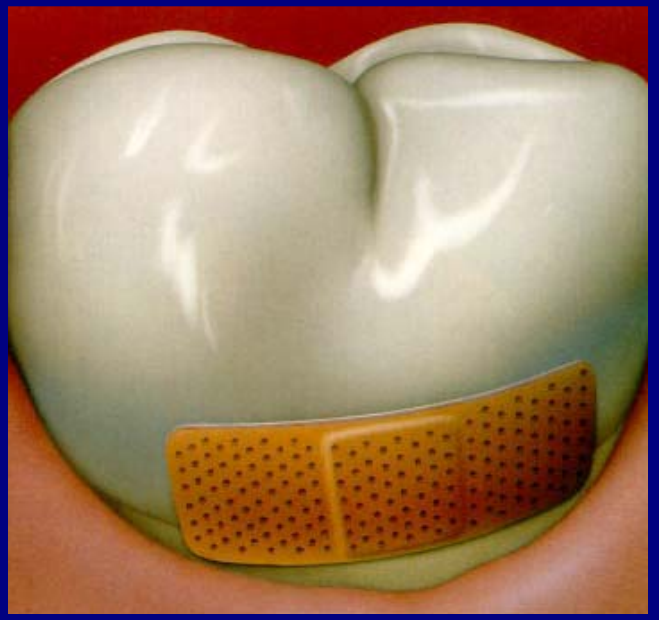
Microcytic Anemia

Lab Findings

- Hb 8-13 or lower
- HCT 20-30%
- Low MCV
- Low MCHC
- Slightly elevated reticulocytes
- Smear dimorphic
  - Normal cells
  - Hypochromic cells
  - Coarse basophilic stippling
- Elevated lead levels

Symptoms Chronic Toxicity: Serum Lead 25-50 mcg/dl

- Dark line (lead sulfide)
  - Gums around the teeth
- Abdominal pain
- Constipation
- Vomiting
- Peripheral neuropathy
- Muscle weakness



Legal Aspects

- Notify OSHA and remove worker
  1. Serum lead > 60
  2. Serum lead > 50 x 3
- Severe poisoning
  1. Coma
  2. Convulsions
  3. Serum lead > 70

Thalassemia

Autosomal Recessive Disorder

Thalassemia

- Microcytosis out of proportion to degree of anemia
- Lifelong
- Family history
- Abnormal RBC morphology
  - Microcytes
  - Acanthocytes
  - Target cells

Thalassemia

- Alpha and beta thalassemia
- Genetic mutations
- Occur in areas where malaria was endemic

Alpha Thalassemia

China, Philippines
Malaysia, Thailand,
Cambodia, Laos,
Vietnam, Burma,
India, Sri Lanka,
African and American
blacks

Alpha Thalassemia

- Silent carrier
- Thalassemia minor
- Hemoglobin H disease
- Hydrops fetalis
  - Incompatible with life

Silent Carrier

- 3 alpha globulin genes, 1 alpha globulin gene affected
- Normal hematocrit
- No clinical or hemoglobin abnormality
- Can only be detected by DNA studies
- No treatment

Alpha Thalassemia Minor (Trait)

- 2 alpha globulin genes normal
- 2 alpha globulin genes affected
- Hct 32-40%
- Hgb normal or decreased
- RBC normal or increased
- MCV below 80
- MCH below 26

Alpha Thalassemia Minor

- Normal hemoglobin electrophoresis
- RBC morphology
  - Microcytosis
  - Hypochromic
  - Aniso/poilokocytosis
- Iron studies normal
- Remember may have a combination of anemias!

Alpha Thalassemia Minor in Pregnancy

- Non-black
  - Screen father of the baby
- Black population
  - Alpha thalassemia major not possible
- Consult for maternal Hb below 10
- If present in both parents
  - Refer for genetic counseling

Hemoglobin H Disease

- One alpha globulin gene normal
- Three alpha globulin genes affected
- Hct 22-32
- Hgb 7-10
- MCV <26
- MCH<80
- Reticulocytosis
  - 5-10%
- Microcytosis
- Hypochromia
- Targeting
- Misshapen red cells
- Hgb electrophoresis
  - 5-30% Hgb H

Symptoms of Hb H Disease

- Hepatosplenomegaly
- Gallstones
- Transfusion-dependent
- Milder in blacks
- Anemia worse during pregnancy
- Refer to physician
- Counseling needed

Alpha Thalassemia Major

- No alpha globin genes are normal
- Hydrops fetalis present
- Does not survive

Beta Thalassemia

- Point mutations rather than large deletions
- Beta0 or Beta+
- Alpha chains unstable
- People of Mediterranean origin
  - Greeks 1:10
  - Italians 1:10
  - Asians 1:25
  - American blacks 1:50

Beta Thalassemia

- Thalassemia major
  - Homozygous B0 or B+
  - <10% Hgb A
- Thalassemia intermedia
  - Mild Homozygous B+
  - < 30% Hgb A
- Thalassemia minor
  - Heterozygous B0
  - Heterozygous B+
  - 80-95% Hgb A

Thalassemia Major

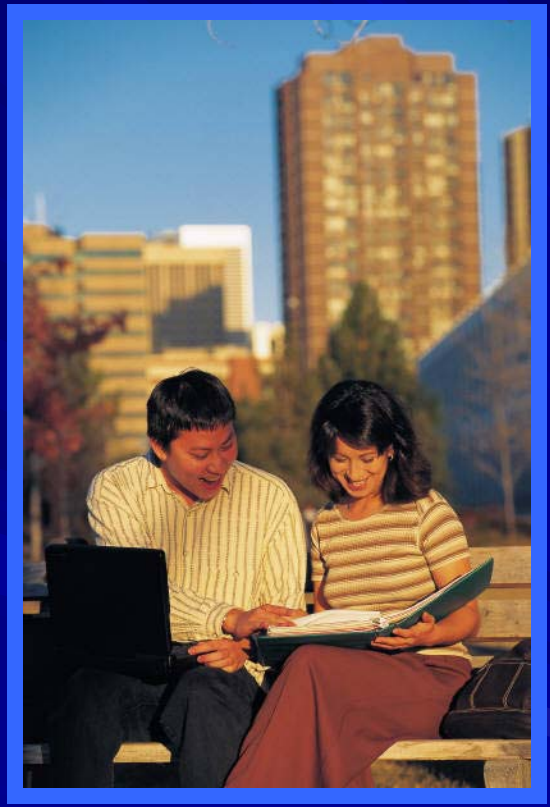
- Severe hemolytic anemia
- Regular transfusion program
- Iron overload (hemosiderosis) common
- Shortened life span

Thalassemia Intermedia

- Blacks may have milder clinical course
- Refer to physician for care

Thalassemia Minor

- Heterozygotic
- Lifelong microcytic, hypochromic anemia
- Severe anemia unusual
- May be asymptomatic
- Splenomegaly?



Thalassemia Minor

- MCV<80
- MCH<26
- Abnormal peripheral smear
- Elevated Hgb F?
- No treatment needed

Thalassemia Minor

- If pregnant, screen father of baby
- Genetic referral if father has hemoglobinopathy
- If coexistent iron deficiency
  - Treat according to protocol

Sideroblastic Anemias

"Sidero" is Greek for Iron

"Blast" is an immature cell

RBCs without Iron

Sideroblastic Anemias

- Can not incorporate iron into RBC
- Lack enzyme
- Genetic, idiopathic, or acquired
  - Drugs or Toxins
- Ringed sideroblasts present in marrow
  (Nucleated, immature RBC with iron granules)
- Hgb 6-10
- Microcytic, normochromic or normocytic, normochromic

B_{12} and Folate Deficiency

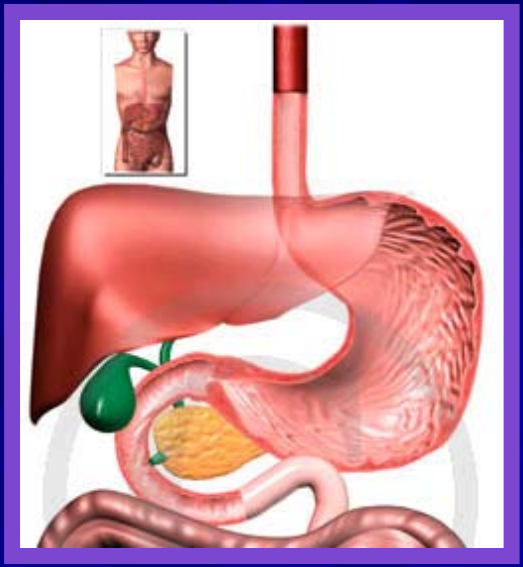
Macrocytic Anemias

Vitamin B_{12}

- Only source is diet
- 3-5 years before deficiency apparent
  - Diet deficiency seen only in vegans
- Bound to intrinsic factor
- Transported to plasma
- Transcobalamin II needed to reach cells

Vitamin B_{12} Deficiency

- Decreased production of intrinsic factor
  - Pernicious anemia
  - Gastrectomy



Vitamin B_{12} Deficiency

- Decreased absorption of B-12
  - Fish tapeworm
  - Blind loop syndrome
  - Surgical resection
  - Cohn's disease
  - Pancreatic deficiency
- Inadequate intake (rare)

Clinical Findings

- Weakness
- Weight loss
- Beefy red tongue (glossitis)
- Numbness
- Ataxia
- Memory loss
- Pallor
- Paresthesias
- Decrease reflexes
- Depression
- Decreased vibration or position sense

Diagnosis

- MCV 110-140
- MCV may be normal in presence of another microcytic anemia
- Macro-ovalocytes, multi-lobed neutrophils
- Diagnosed through serum B-12<100 pg/L
  - Shilling test
    - Decreased absorption of B-12
- Differentiate from folate deficiency

B_{12} Deficiency

- Gradual development over 1-3 years
- Treatment (Cyanocobalamin)
  - LD: 100mcg/d IM x 3-5 days
  - MD: 100mcg IM q2-4 weeks

B_{12} Deficiency

- Response rate
  - Reticulocytes and RBCs
    - Similar to iron deficiency
  - Neurologic signs and symptoms
    - 6-12 months (If less than 6 months duration)
  - Other signs and symptoms
    - 1-2 weeks

Folate Deficiency

- Clinical findings: similar to B12 deficiency
- No neurologic findings
- Macro-ovalocytes
- Hypersegmented neutrophils
- Normal serum B_{12}
- Reduced folate

Folate Deficiency

- Daily requirements
  - 50-100 mcg
- Dietary deficiency most common cause
- Diagnosis
  - RBC folate test of choice
- Gradual development of anemia
  - 1-5 months
- Treatment
  - 1mg/day po x 2-3 weeks

Causes of Folate Deficiency

- Dietary deficiency
- Decrease absorption
  - Topical sprue
  - Drugs
    - Phenytoin, Sulfas

Causes of Folate Deficiency

- Increased requirement
  - Chronic hemolytic anemia
  - Pregnancy
  - Exfoliative skin disease
- Loss of folate
  - Dialysis
- Inhibition of reduction to active form
  - Methotrexate

Other Causes of Macrocytosis

- HIV treated with zidovudine
- Hypothyroidism
  - Mild macrocytosis
- Alcoholism
  - Folate deficiency and liver disease
  - Target cells in peripheral blood

Sickle Cell Trait

Autosomal Dominant Anemia

Sickle Cell Trait

- One gene normal hemoglobin
- One gene for hemoglobin S
- 34-54% hemoglobin S
- Rarely anemic
- Blacks - 8%
- Also in Africans, Italians, Indians

Associated Conditions

- Bacteruria
- Hematuria
- Hyposthenia
  - Diminished strength
- Splenic infarction
  - High altitude

Symptoms

- Generally asymptomatic
- History of bladder/kidney infections
- May confuse diagnosis of other coexisting anemia
- Diagnosed by Hb electrophoresis
  - 34-54% Hb S
  - Sickledex positive
  - Normal iron studies

Plan of Care

1. Screen all black pregnant women
   - If positive for trait, screen father of baby
2. No treatment needed for trait alone
3. Pregnant women with sickle cell trait
   - Urinalysis and culture each trimester
   - Educated on S/S UTI
   - Genetic counseling if father has hemoglobinopathy

Image acknowledgments:

- **Black, McKay, Braude, Jones, & Margesson (2002) *Obstetric and Gynecologic Dermatology***
- **Pathguy.com**
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