Anemias

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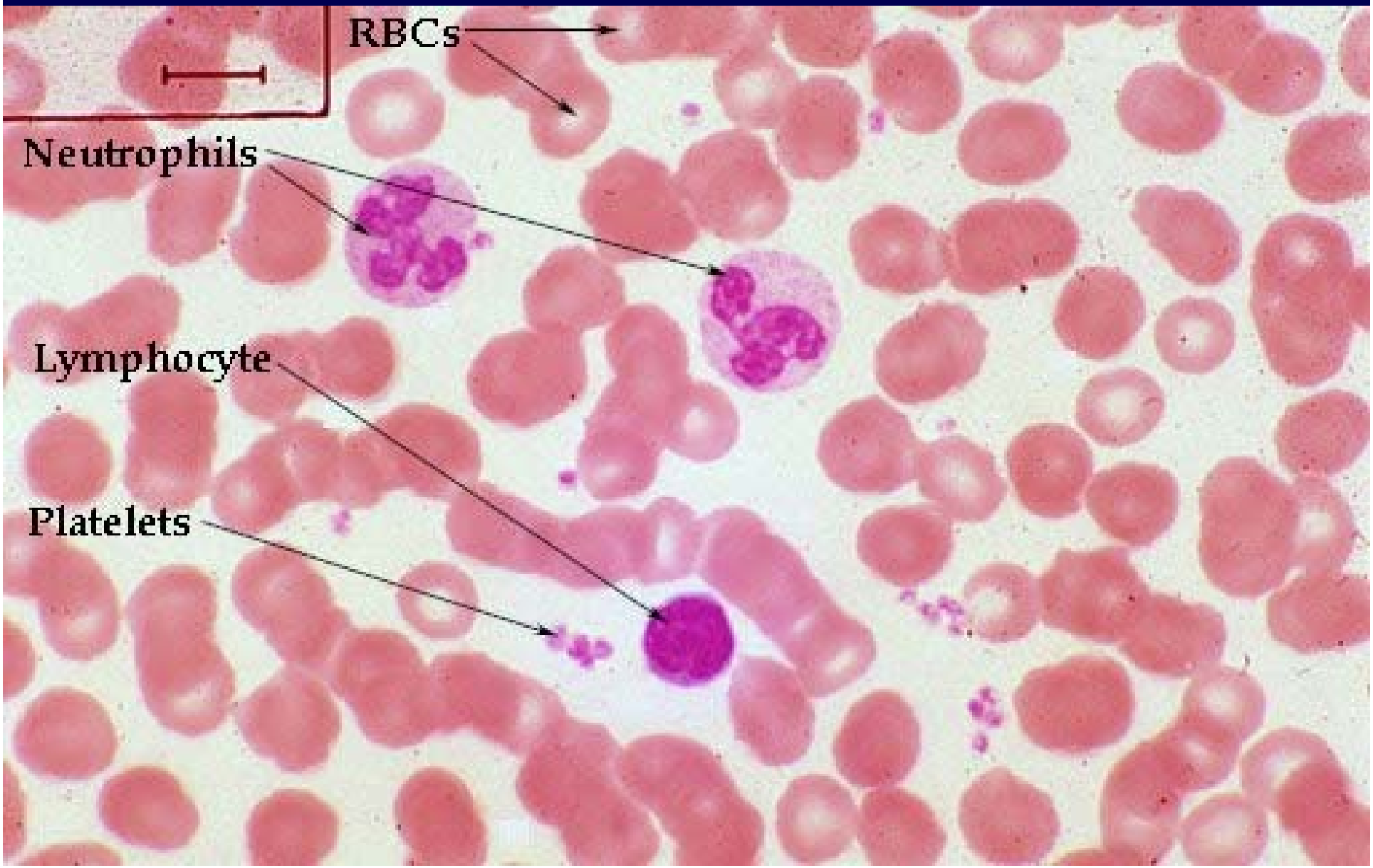
Anemia-Pharmacist Roles

- Community Pharmacist
  - Iron deficiency
  - B12 and folic acid
- Hospital Pharmacist
  - Chemotherapy induced anemia
  - Dialysis
  - Hemolytic anemia

Peripheral Smear



Anemia-Definitions

- **Anemia: Decreased RBC**
- **Erythrocytosis: Increased RBC**

Anemia Grade (Hemoglobin in g/dL)

Grade	Severity	NCI Scale	WHO scale
0	None	Normal*	>11
1	Mild	10-normal	9.5-10
2	Moderate	8-10	8-9.4
3	Severe	6.5-7.9	6.5-7.9
4	Life-threatening	<6.5	<6.5

- WHO < 13 g/dL for men; < 12 g g/dL women
- 12-16 g/dL for women, 14-18 g/dL for men

Consequences of Anemia

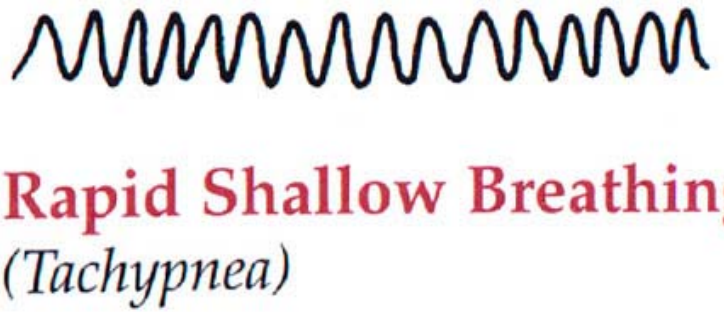
- Pallor
- Fatigue
- Shortness of breath
- Worsening of cardiac disease
- Cardiac Arrest
- Shock
- Death

Cardiovascular

- Tachycardia
- Hypotension
- Mild cardiac enlargement
- Functional systolic murmurs
  - Systolic murmur
  - Diastolic murmur uncommon
  - Roaring in ears (tinnitus), especially at night
- High output failure (if anemia severe)
- Worsening of heart failure or other CV disease

Pulmonary

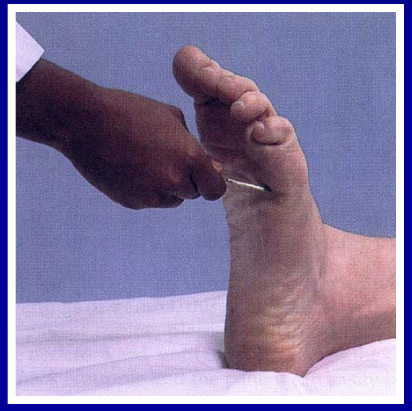
- Exertional dyspnea
- Orthopnea
- Tachypnea

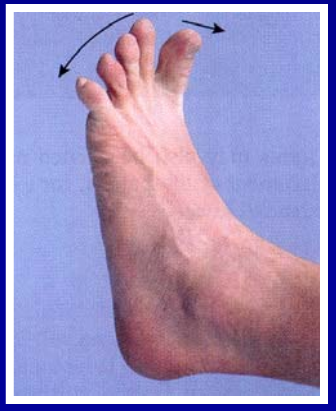


Rapid Shallow Breathing
(*Tachypnea*)

Neurologic

- Confusion
- Headache
- Fainting
- Light-headedness
- Peripheral nerve paresthesia
- Positive Babinski and Romberg signs
- Decreased balance, ataxia
- Decreased positional sense
- Deep tendon reflexes
- Intolerance to cold

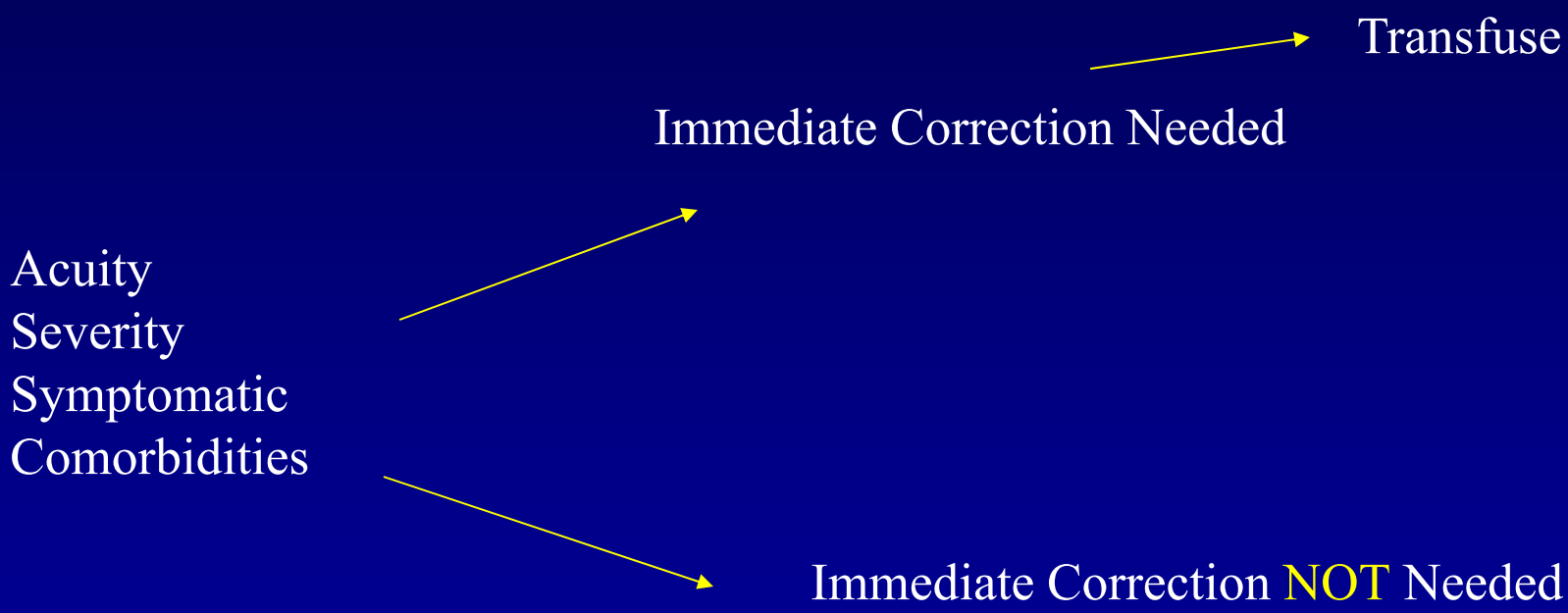




Managing Anemia

- Determine Acuity
- Determine Etiology
- Initiate Therapy

Anemia Management-Determine Acuity



Transfusion of RBC

Benefit

- Immediate increase of 1g/dL Hg per unit infused, regardless of etiology

Risk

- Infection
- Transfusion reactions

Process

- Informed Consent
- Type and Cross
- Premed with Acetaminophen and Diphenhydramine
- Infuse 1 Unit over 4 hours

Managing Anemia

- Determine Acuity
- Determine Etiology
- Initiate Therapy

Laboratory Evaluation

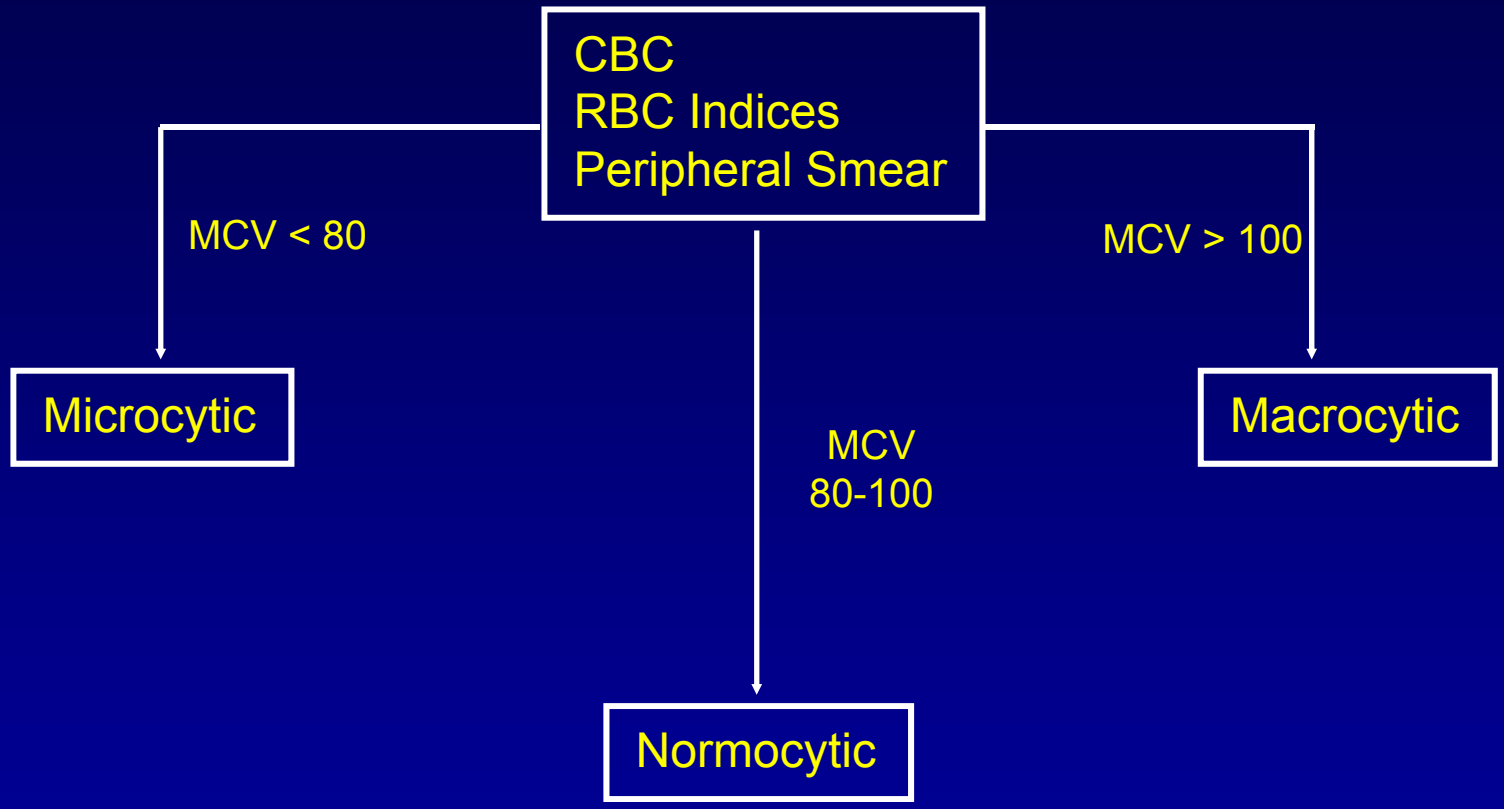
1. **Initial screening**

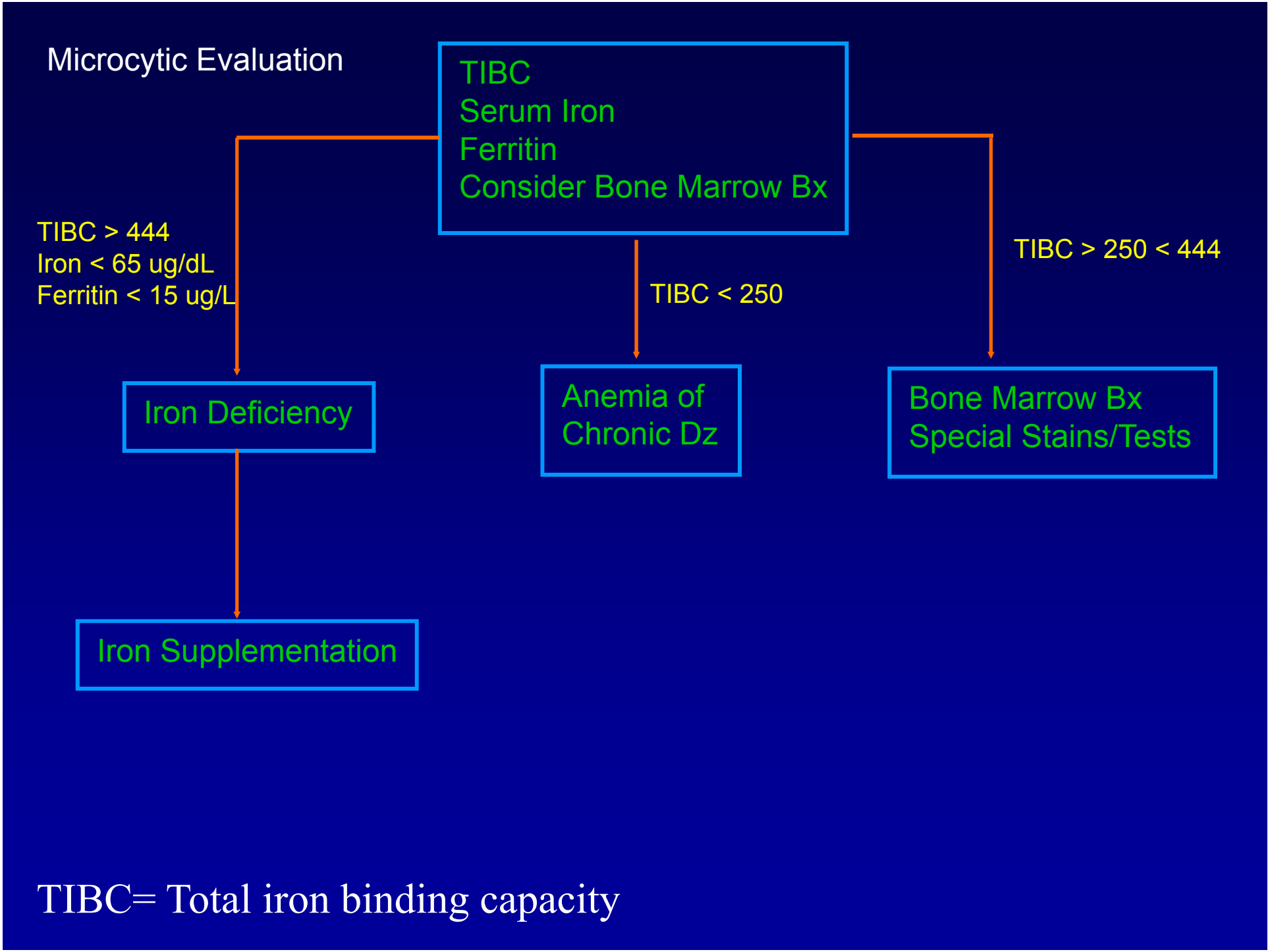
   HgB

   HCT

   MCV

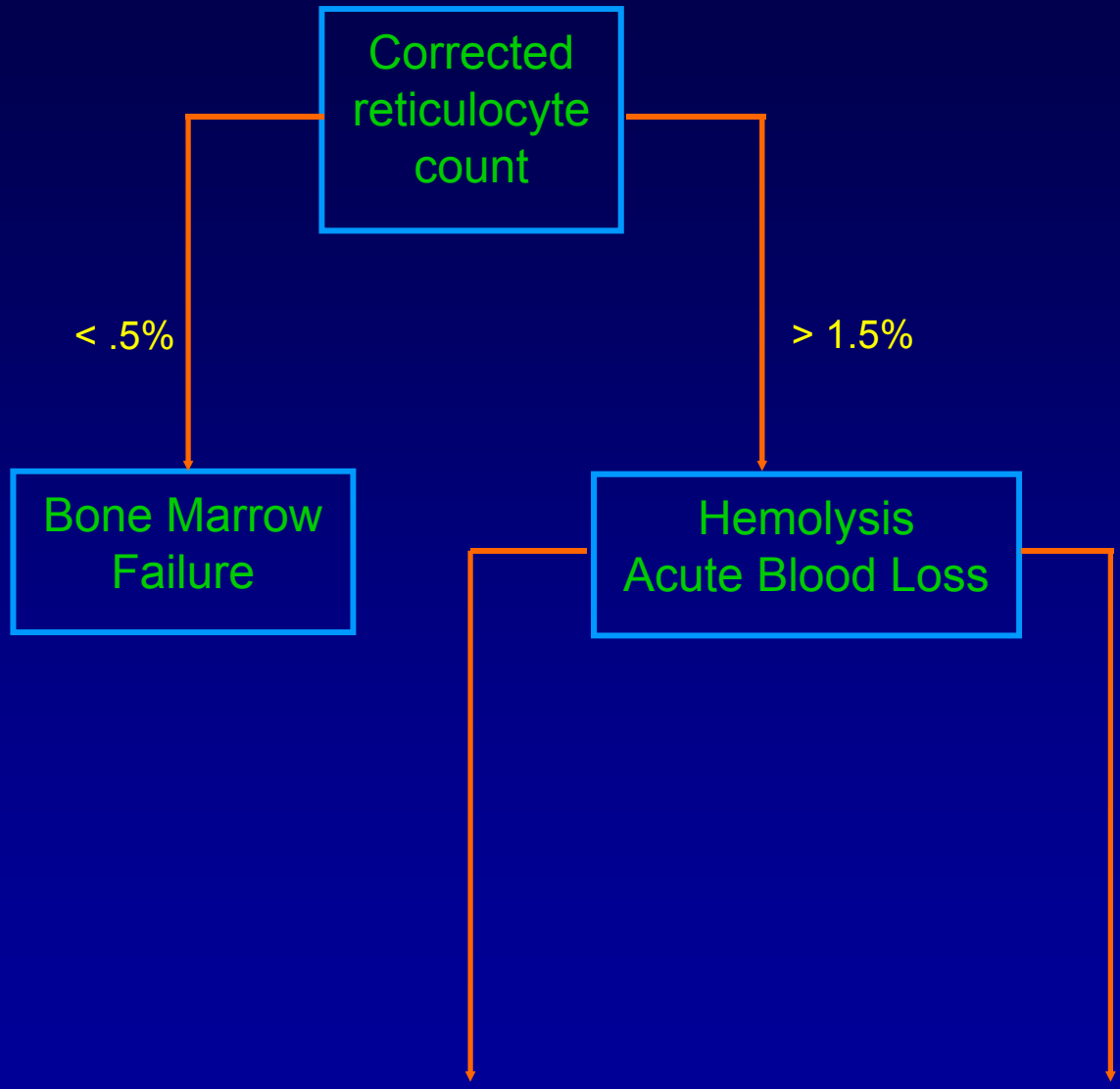
Laboratory Evaluation

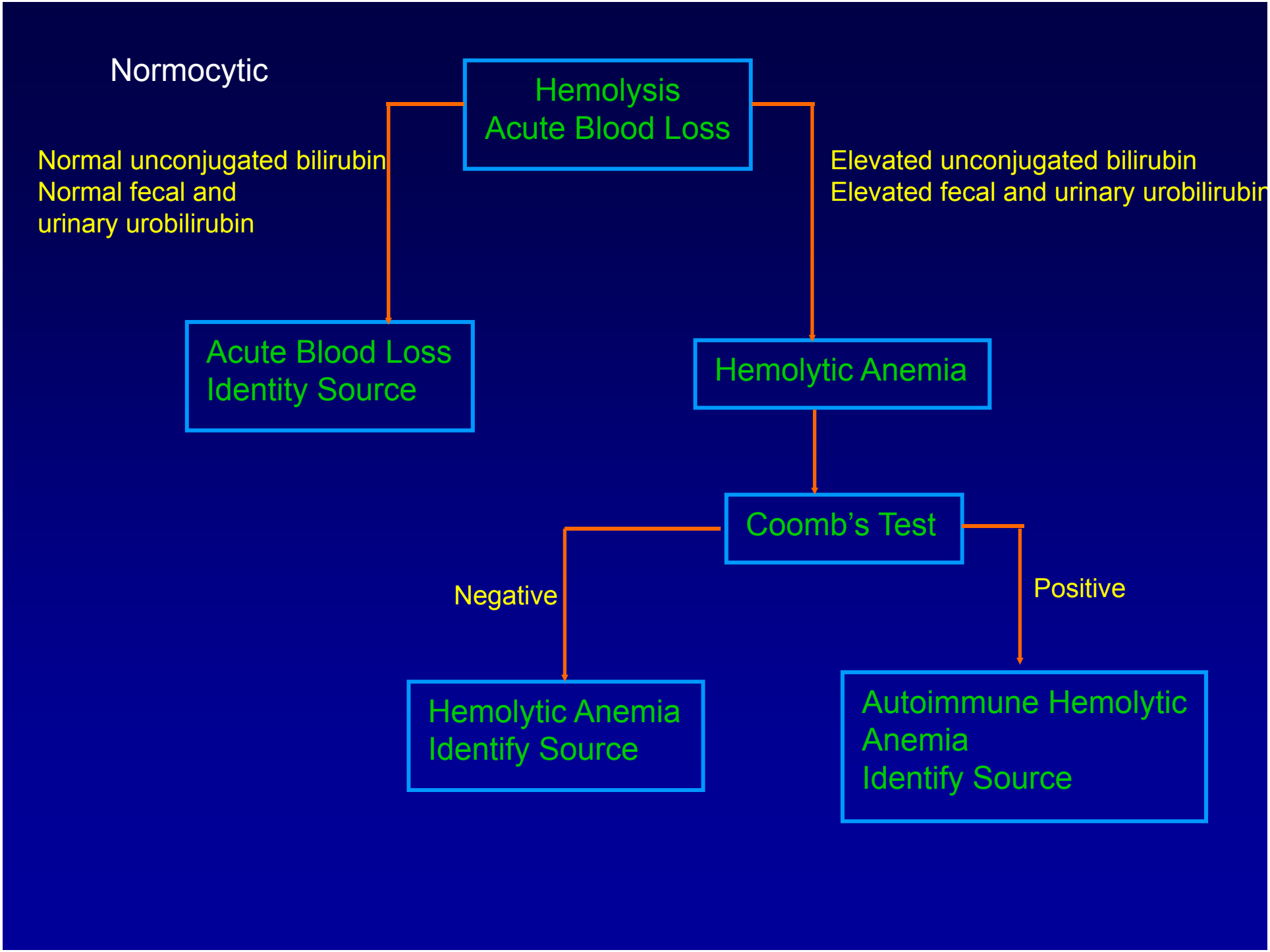


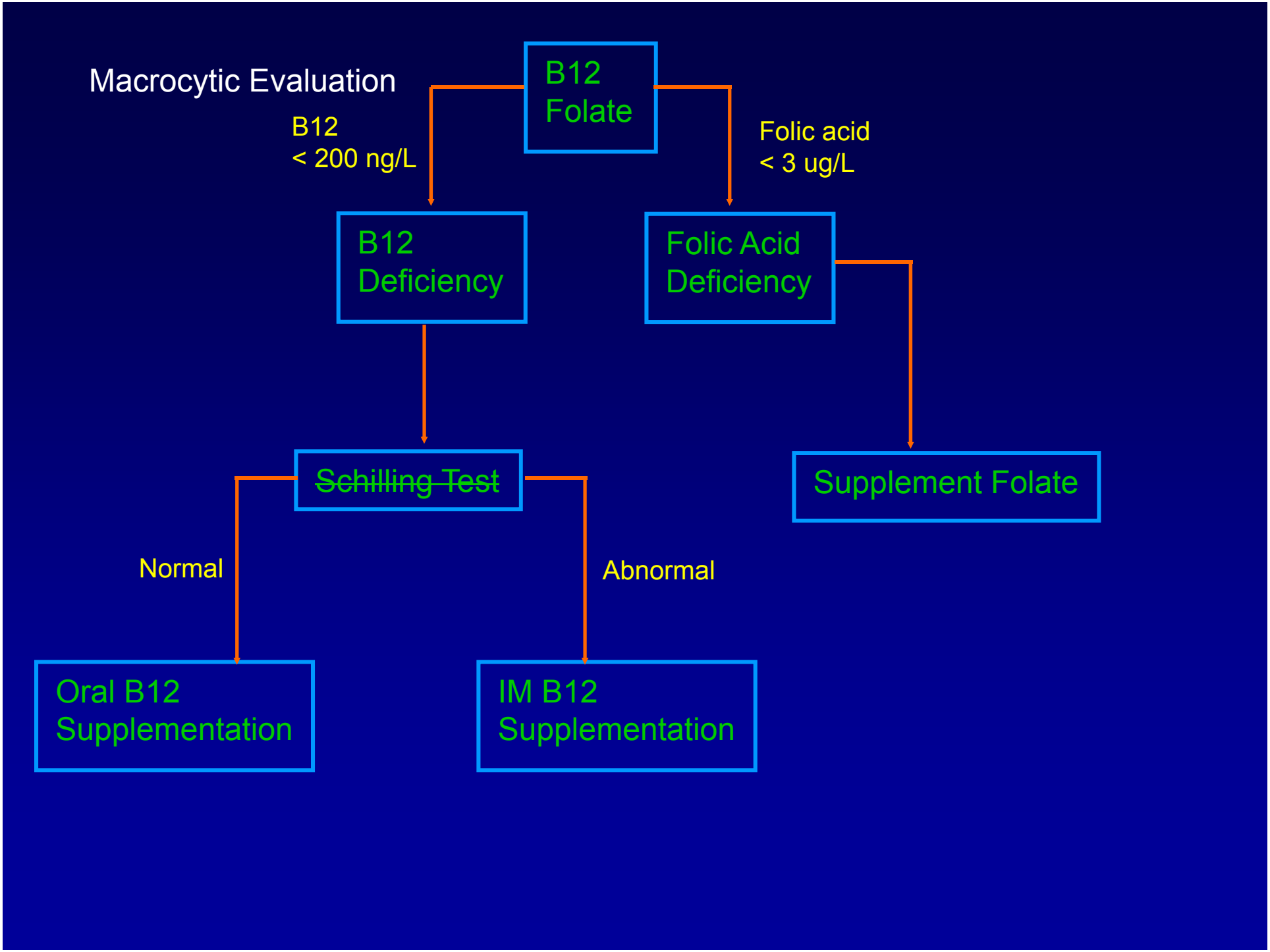


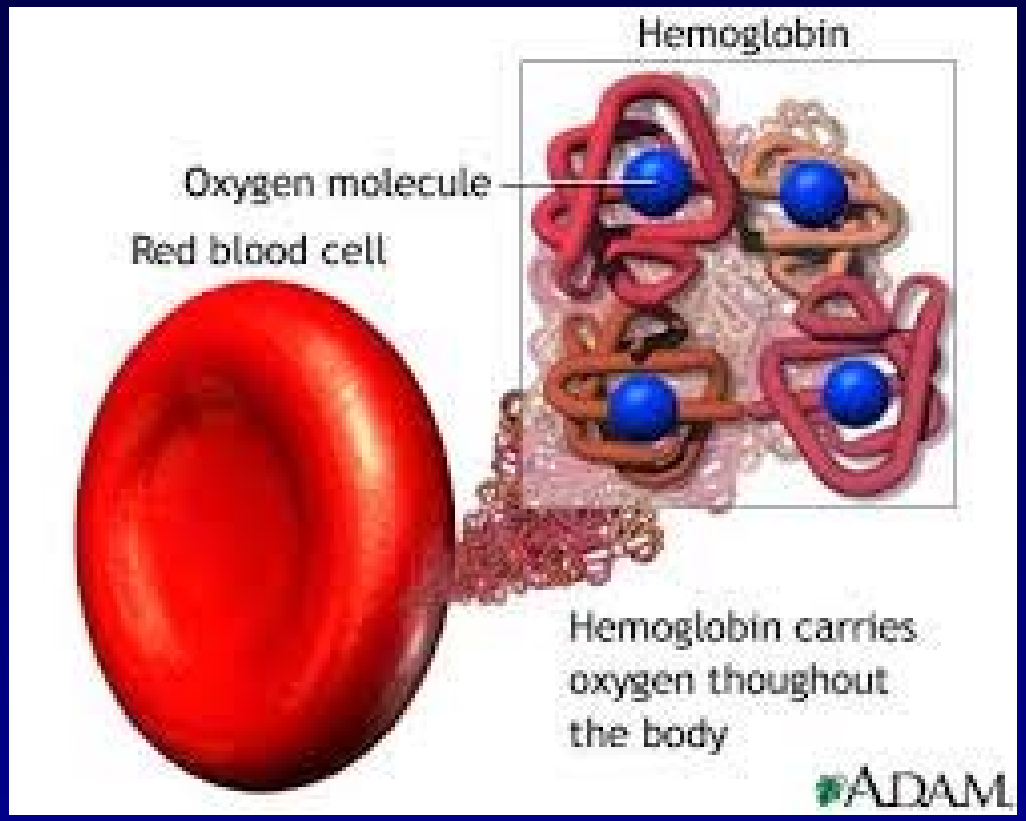
TIBC= Total iron binding capacity

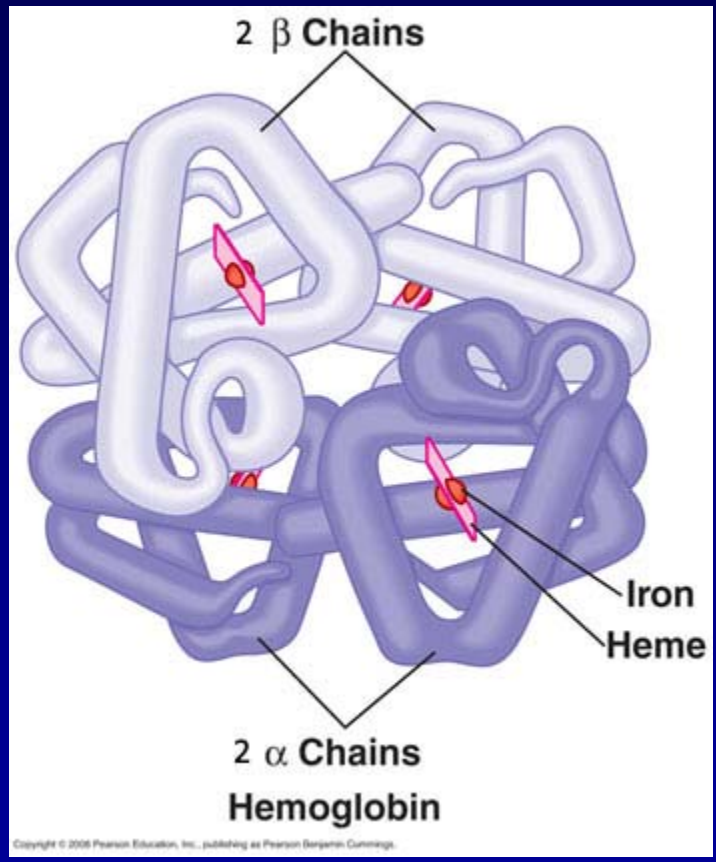
Normocytic Evaluation: Determine whether bone marrow is working




Normocytic
Hemolysis
Acute Blood Loss
Normal unconjugated bilirubin
Normal fecal and
urinary urobilirubin
Elevated unconjugated bilirubin
Elevated fecal and urinary urobilirubin
Acute Blood Loss
Identity Source
Hemolytic Anemia
Coomb's Test
Negative
Positive
Hemolytic Anemia
Identify Source
Autoimmune Hemolytic
Anemia
Identify Source


Macrocytic Evaluation
B12
Folate
B12
< 200 ng/L
Folic acid
< 3 ug/L
B12
Deficiency
Folic Acid
Deficiency
Schilling Test
Supplement Folate
Normal
Abnormal
Oral B12
Supplementation
IM B12
Supplementation


Hemoglobin
Oxygen molecule
Red blood cell
Hemoglobin carries oxygen thoughout the body
A.D.A.M.


2 β Chains
Iron
Heme
2 α Chains
Hemoglobin

Iron

- **Total body stores 4 g**
- **Oral intake is 6mg/1000 kcal, 10% absorbed**
- **Fe^{+3} (ferric, nonabsorbed)**
- **Fe^{+2} (ferrous, absorbed)**

Daily Iron Requirements

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	0.27 mg*	0.27 mg*		
7–12 months	11 mg	11 mg		
1–3 years	7 mg	7 mg		
4–8 years	10 mg	10 mg		
9–13 years	8 mg	8 mg		
14–18 years	11 mg	15 mg	27 mg	10 mg
19–50 years	8 mg	18 mg	27 mg	9 mg
51+ years	8 mg	8 mg		

* Adequate Intake (AI)

Table 1 lists the current iron RDAs for nonvegetarians. The RDAs for vegetarians are 1.8 times higher than for people who eat meat. This is because heme iron from meat is more bioavailable than nonheme iron from plant-based foods, and meat, poultry, and seafood increase the absorption of nonheme iron

Treatment - Iron Deficiency Anemia

Salt	Elemental Iron (%)
Ferrous sulfate	20
Ferrous sulfate exsicated	30
Ferrous gluconate	12
Ferrous fumarate	33
Ferric pyrophosphate	12
Ferrous carbonate	43

Oral Iron therapy

- Ferrous sulfate 20% 60-65mg
- Ferrous gluconate 12% 37-39mg
- Ferrous fumarate 33% 33mg

Iron

Iron (Ferrous sulfate)	
Mechanism	Replaces iron, found in hemoglobin, myoglobin, and other enzymes; allows the transportation of oxygen via hemoglobin
Indication	Prevention and treatment of iron-deficiency anemias
Common Off Label Use	None
Efficacy	Resolution of anemia
Dosing	Treatment: 300mg bid-qid Prevention: 300mg qd
Dose Adjustments	Not required
Med safety	Dozens of formulations and concentrations! Iron overdose leading cause of poisoning in children

Iron (Ferrous sulfate)	
Contraindications	hemochromatosis, hemolytic anemia
Black Box Warnings	None
Common Adverse Effects	• GI distress, nausea, constipation etc
Rare but Serious Adverse Effects	Overdose can be fatal
Drug Interactions	• Antacids, H2 antagonists and PPIs decrease absorption • Vitamin C enhances absorption • Coffee, tea, dairy (Calcium), soy decrease absorption (avoid)
Clinical Pearls	• Causes discoloration of stools (black) • Interferes with fecal occult blood tests • Liquid formulation is impossible to remove from clothes • Avoid sustained release products (ineffective)

Outcome Evaluation-Efficacy

- Reticulocytosis occurs within 7-10 days
- HgB increases 1g/dL per week
- Requires 3-6 months of therapy

Outcome Evaluation - Toxicity

- Discoloration of feces
- Nausea
- Diarrhea or constipation

Intravenous Iron Administration

- Iron malabsorption
- Intolerance
- Noncompliance
- Refuse transfusion

Intravenous Iron Dosing

Iron Deficiency Anemia

- Mg iron = W x (100-%Hg) x 0.3
- Where *W* is the patient's weight in pounds and %Hb is the patient's observed hemoglobin expressed as a percentage of the normal hemoglobin concentration (assuming 14.8 g of hemoglobin per 100 mL is equivalent to 100% concentration).
- If the patient weighs 13.6 kg (30 lb) or less, the dose is 80% of the calculated amount.

Blood Loss

- Mg of iron = blood loss x hematocrit

- Where blood loss is in milliliters and hematocrit is expressed as a decimal fraction.

Iron Dextran

- IM via the Z-tract method

  100 mg/injection

- IV

  Multiple undiluted injections

  Single diluted

Two Newer IV Iron Products

- Ferrlecit = Sodium ferric gluconate complex in sucrose
  - Marketed in Europe for over 40 years, entered US market in 1999
  - 62.5mg elemental iron in 5ml sucrose
- Venofer- Iron Sucrose
  - Marketed in Europe for over 30 years, entered US market in 2000
  - 100mg elemental iron in 5ml water

Comparison

	Iron Dextran	Ferrlicet	Venofer
Safety-Anaphylaxis	8.7 allergic episodes/million doses	3.3 allergic episodes/million doses	No reaction in 7/7 patients with prior anaphylaxis to iron dextran
Safety-Overall	26% with any toxicity 3% with severe 0.6% life threatening	Hypotension, rash, flushing, GI in 10-20%	Very well tolerated, diarrhea, GI, minty taste in less than 5%
Test Dose	Yes	No	No
IM	Yes	No	No

B12 Deficiency: Etiology

Dietary intake of B12 requires many factors

- Acid-pepsin in the stomach to liberate B12 from binding to proteins
- Pancreatic proteases to free B12 from binding to R factors
- Secretion of intrinsic factor (IF) by the gastric parietal cells to bind to B12
  - Pernicious anemia
- An intact ileum with functional B12-IF receptors
  - Gastrectomy or other malabsorption syndromes

B12

B12 (Cyanocobalamin)	
Mechanism	Coenzyme for various metabolic functions, including red blood cell maturation
Indication	Prevention and treatment of B12 deficiencies which result in macrocytic anemias
Common Off Label Use	None
Efficacy	Resolution of anemia
Dosing	Oral: 1000-2000 mcg daily for 1-2 weeks; maintenance: 1000 mcg daily IM: 1mg a day x 1 month, then 100mcg per month Intranasal (Nascobal): 500 mcg in one nostril once weekly
Dose Adjustments	Not required
Med safety	

B12	
Contraindications	None
Black Box Warnings	None
Common Adverse Effects	• Anxiety, dizziness • Worsening of cardiovascular disorders
Rare but Serious Adverse Effects	None
Drug Interactions	• None
Clinical Pearls	Vegan diets can result in B12 deficiency Alcoholics Pregnancy with increased B12 need Some SC formulation contain aluminum or benzyl alcohol, avoid in neonates

Folic Acid Deficiency-Etiology

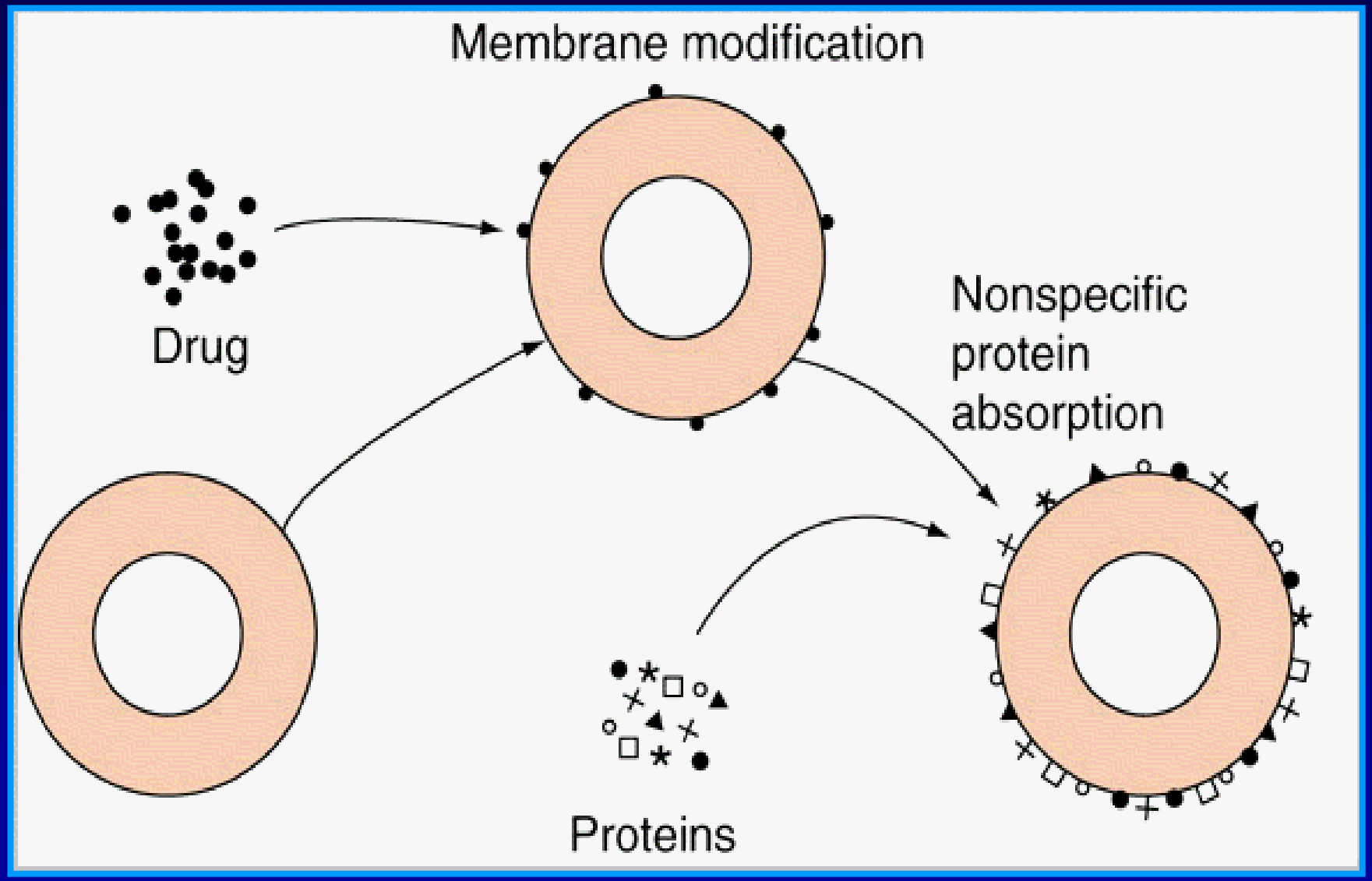
- Poor dietary intake
  - Alcoholism
- Decreased absorption
- Hyperutilization
  - Pregnancy
- Inadequate utilization
- Drugs
  - Methotrexate inhibits the enzyme dihydrofolate reductase, which is needed for regenerating folate during DNA synthesis
  - Phenytoin (inhibits absorption)

Folic Acid

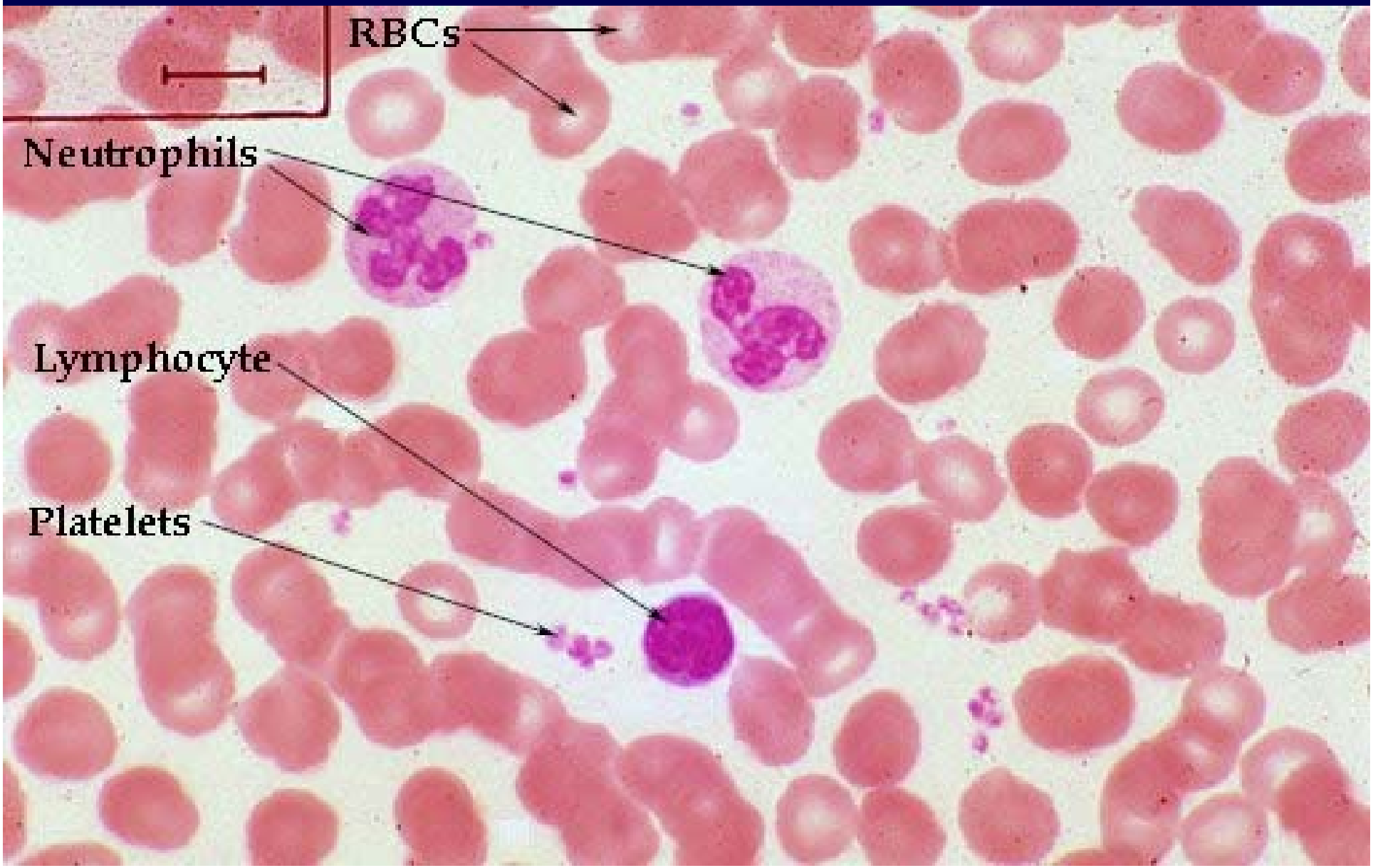
Folic Acid	
Mechanism	Coenzyme for various metabolic functions particularly for purine and pyrimidine synthesis, including red blood cell maturation
Indication	Treatment of megaloblastic and macrocytic anemias due to folate deficiency; dietary supplement to prevent neural tube defects
Common Off Label Use	Alternative to leucovorin for methotrexate toxicity
Efficacy	Resolution of anemia
Dosing	Anemia: Oral, I.M., I.V., SubQ: 0.4 mg/day Pregnant and lactating women: 0.8 mg/day
Dose Adjustments	Not required
Med safety	Confused with folinic acid (leucovorin)

Folic Acid	
Contraindications	None
Black Box Warnings	None
Common Adverse Effects	• Flushing, malaise • Worsening of cardiovascular disorders
Rare but Serious Adverse Effects	None
Drug Interactions	• Decreases therapeutic effect of methotrexate, pemetrexed
Clinical Pearls	In US breads, corn meal etc are enriched with folic acid to decrease risk of neural tube defects Some formulations contain benzyl alcohol, avoid in neonates

Hemolytic Anemia

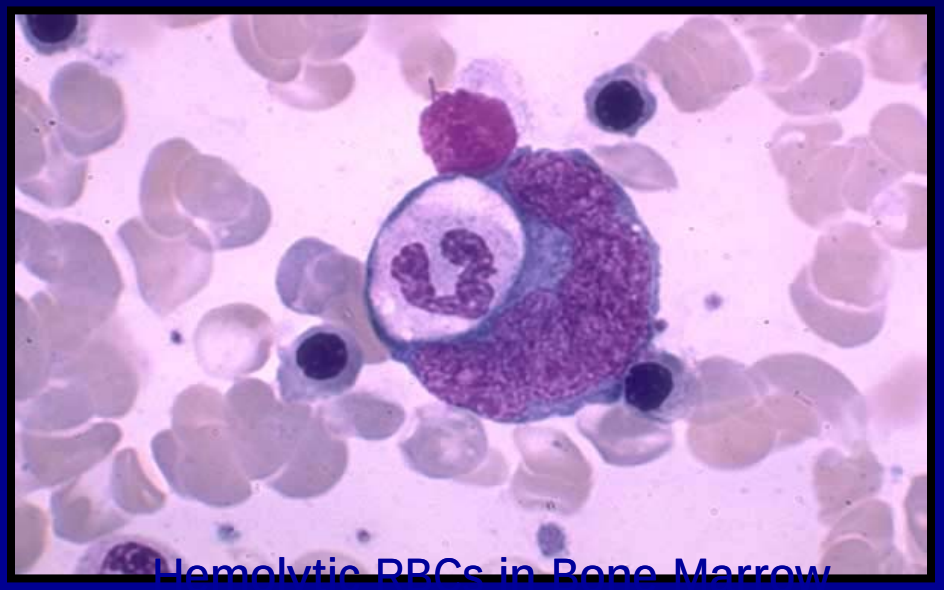


Peripheral Smear

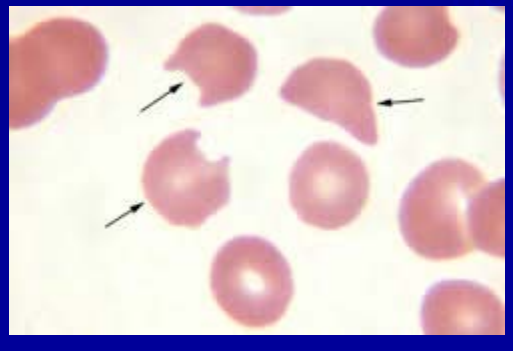


Hemolysis

- Destruction of RBCs by therapy
- Destruction of RBCs by body's own defenses, infection, systemic disease
- Incompatible blood transfusions, drug reactions



Hemolytic RBCs in Bone Marrow



Hemolytic Anemia

Drugs Associated with Hemolytic Anemia

- Dapsone
- Methyldopa
- Penicillins
- Sulfonamides

Treatment of Drug Induced Hemolytic Anemia

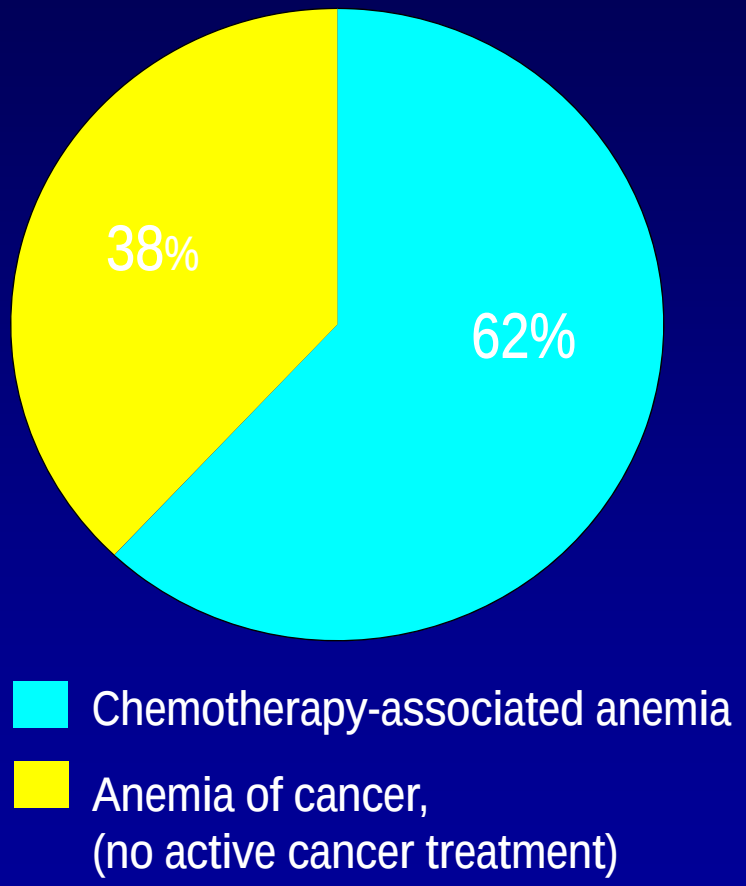
- Stop drug
- Steroids

Cancer-Associated Anemia

Causes

- Therapy (chemotherapy, radiation, surgery)
- Bone marrow tumor involvement
- Nutritional deficiencies
- Hypersplenism
- Anemia of Chronic Disease
- Blood loss
- Hemolysis

Prevalence*



Cancer Treatment Reviews 2000;26:303-11. BMJ 2001;84(S1):31-7. Adapted from Groopman JE and Itri LM. J Natl Cancer Inst. 1999;91:1616-1634; HCIA Inc., 1998.

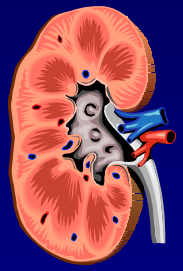
Treatment Options

- No Therapy
- Correct obvious causes (e.g. nutritional deficiencies, bleeding, etc.)
- Red Cell Transfusion
  - Adverse events (fever, urticaria, hepatitis C, CHF)
  - Infection transmission
  - Shortage
- Erythropoietic Growth Factors
  - Epoetin alfa (Procrit®, Epogen®), rHuEPO
  - Darbepoetin alfa (Aranesp®), NESP (Novel erythropoiesis stimulating protein)

Consider Iron if:
- Ferritin <100 ng/ml
- Iron <70 mcg/dL
- Transferrin Sat. <20%

Erythropoietin Feedback Mechanism to Control Red Blood Cell Production

Decreased oxygen delivery to the kidneys

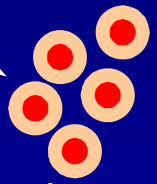


Peritubular interstitial cells detect low oxygen levels in the blood

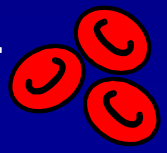
Peritubular interstitial cells secrete erythropoietin (EPO) into the blood

EPO

Pro-erythroblasts in red bone marrow mature more quickly into reticulocytes



More reticulocytes enter circulating blood



Larger number of red blood cells (RBCs) in circulation

Increased oxygen delivery to tissues

Return to homeostasis when response brings oxygen delivery to kidneys back to normal

Dosing	Indications	Adverse Effects (Common)	Adverse Effects (Rare)
Epoetin 40,000 units q week Darbepoetin 500 mcg SubQ q 3 weeks	Chronic kidney disease (IV administration preferred) Chemotherapy induced anemia	Hypertension Edema	Thrombosis CV events Cancer progression Pure red cell aplasia

Clin J Am Soc Nephrol. 2012 Feb; 7(2): 348–353.

For patients with CKD not on dialysis, consider initiating ESA treatment only when the hemoglobin level is less than 10 g/dl and the following considerations apply.

The rate of hemoglobin decline indicates the likelihood of requiring a red blood cell transfusion.

Reducing the risk of alloimmunization and/or other red blood cell transfusion-related risks is a goal.

If the hemoglobin level exceeds 10 g/dl, reduce or interrupt the dose of ESA and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions.

For patients with CKD on dialysis

Initiate ESA treatment when the hemoglobin level is <10 g/dl.

If the hemoglobin level approaches or exceeds 11 g/dl, reduce or interrupt the dose of ESA.

When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, and then monitor at least monthly.