Anemia Review For Nurse Practitioners

GOALS: Upon completion of this presentation, participants will be able to:

1. Generate a short differential list specific to the findings of the complete blood count (CBC).
2. Explain further diagnostic tests based on a rational approach to the differential.
3. Plan treatment for the most common forms of anemia.

I. BACKGROUND:

- Anemia is **NOT** a disease! It is a working diagnosis.
- *Definition:* reduction in either the volume of the red blood cells (HCT) or in the concentration of hemoglobin (<95% of normal distribution)
- *Physiologic definition:* blood lacks the ability to adequately oxygenate tissues.
- *Classic laboratory definition:* HGB < 12 in women; HGB < 14 in men.
  - This definition leads to a high frequency of diagnosis of anemia in elderly.
    - In 21% of elderly women, 34% of elderly men, cause was found in *only 10%*
    - May be better to classify as high, moderate, or low risk of *significant anemia*.
      - Men: high risk if <12, moderate risk if 12-14, low risk if >14
      - Women: high risk if <10, moderate risk if 10-12, low risk if >12
    - Using these criteria 6-10% at moderate risk, 1-2% high risk
  - Relative anemias: those who might or might not be anemic but don't fit the classic definition
    - Smoker who drops his HCT
    - Prolonged stasis with venipuncture → hemoconcentration
    - Ambulation after recumbancy may decrease plasma volume by 10%
    - Pregnancy: plasma volume increases more than red cell mass (nadir ~28 weeks EGA)

II. EVALUATION

A. History

1. <u>Is the patient truly anemic?</u>

a) Volume overload → as in CHF, iatrogenic fluid overload

b) Sequestration → splenomegaly

c) Hypersplenism → rbc destruction

d) Diminished volume → burns

2. <u>Acquired vs. hereditary anemia?</u>

a) Family history of anemias

b) Inherited anemias- G6PD deficiency, SS, thalassemias, spherocytosis

3. <u>Is there other blood loss?</u> (Note: *Iron deficiency = blood loss until proven otherwise)*

a) GI losses, menstruation, pregnancy

b) Other: diagnostic phelbotomy, frequent blood donation, soft tissue hematomas and fractures (esp. elderly hips), urinary, pulmonary hemosiderosis, hemostatic defects

3. Is there evidence of medication or toxin exposure?

a) Alcohol #1; occupational exposure ~ lead exposure
SPECIFIC MEDICATIONS:

b) *Drugs causing marrow suppression*
- **i.** Antineoplastics
- **ii.** Antibiotics: sulfas, chloramphenicol, streptomycin, quinacrine
- **iii.** Anticonvulsants: Dilantin, Tegretol, carbamazipine
- **iv.** Anti-inflammatories: gold salts, aspirin
- **v.** Oral hypoglygemics : chlorpropamide, tolbutamide
- **vi.** Tranquilizers: Librium, Thorazine, Compazine
- **vii.** Antihistamines: chlorpheneramine, triplennamine

c) *Drugs causing hemolysis*
- **i.** In G6PD deficiency: sulfas, primaquine, quinacrine, nitrofurantoin, pyridium
- **ii.** Immune hemolytic anemias: penicillin, sulfas, quinine, quinidine, Aldomet, levodopa

d) *Drugs causing folate antagonism:*
- **i.** Methotrexate, Fansidar, Bactrim, triamterene (Maxide/Dyazide)
- **ii.** Porphyrin heme synthesis antagonists: alcohol, isoniazid (INH)

e) *Drugs causing GI blood loss:*
- **i.** Alcohol
- **ii.** Anti-inflammatories (aspirin, NSAIDs, cox-2 inhibitors)

B. Physical Findings associated with Anemia

- Skin: pallor (pallor of palmar creases = HGB<7), jaundice, petechiae, telangectasia, & spider nevi.
- Eyes: scleral icterus → hemolysis; retinal hemorrhage → bleeding disorders
- Mucous membranes: pallor; glossitis → pernicious anemia
- Lymph: adenopathy → malignancy or infection
- Cardiac: flow murmurs at LSB; venous hum; widened pulse pressure
- Abdomen: splenomegaly, hepatomegaly
- Pelvic/Rectal: hemmorrhoids → blood loss; masses → malignancy
- Neuro: diminished vibrations, dementia → B12 deficiency

C. Laboratory tests

1. Lab Pitfalls

- Too small a needle → hemolysis
- Tourniquet too tight → hemoconcentration
- Tourniquet too long → hemoconcentration

- Tube too warm (room temp or ↑) → RBC's swell → raises HCT and MCV

3. **Best technique**
   - Transfer from syringe to clean vacuum tube (avoid opening vacuum tube seal) → prevents air hemolysis
   - Prepare blood smears immediately
   - Heparin tube → best to prevent hemolysis (does *not* affect MCV/HCT)
   - EDTA tube → best for counts/morphology if smears are not from fresh blood
     - Also best to prevent clumping

4. **Common Useful Lab Tests**

   a) **CBC (include WBC and platelet count)**
      - Pancytopenia → bone marrow disease, megaloblastic anemia

   b) **HGB/HCT**
      - Hgb more reliable indicator of O2 capacity than HCT or RBC count; especially with markedly elevated WBC → falsely elevated HCT
      - Hyperglycemia → falsely elevated HCT (cell swelling)
      - Males have higher HCT with onset of androgens → hematopoesis
      - Aging may decrease HCT slightly
      - HCT increased at alltitudes above 4000 ft
      - Smoking one pack/day increases HCT by 1.5% (as if living at 5000 ft)

   c) **MCV: Mean Corpuscular Volume**
      - Measure of average rbc volume
      - Useful in classification into micro, normo, macrocytic anemias

   d) **RDW: Red Cell Distribution Width**
      - Non-specific measure of *variability* of red blood cell size
      - Fairly sensitive screening test for iron deficiency in general population (especially in kids, not as useful in hospitalized patients)

   e) **MCHC: Mean Corpuscular Hemoglobin Concentration**
      - Measure of average rbc hemoglobin load
      - If markedly elevated (>35) think spherocyctosis/chronic hemolysis

   f) **Reticulocyte count**
      - *Not* part of automated CBC, counted after Wright's stain of peripheral smear
      - Reflects the ability of the bone marrow to respond to anemia
      - Count must be corrected for level of anemia
        - Index = retic count X patient's HCT/45
        - Hallmark of hemolytic anemia: persistance of retic count >5% suggests ongoing hemolytic process

- Retic count < 0.5% in face of anemia suggests primary bone marrow suppression

g) Ferritin: the storage form of iron

- highly <u>specific</u> for iron deficiency/low sensitivity (high false negative rate)
- expensive and not always readily available
- better than TIBC/serum iron for diagnosis of iron deficiency
- low in iron deficiency; normal in anemia of chronic disease

h) Transferrin: the "commuter" form of iron going from gut to ferritin to rbc

- reported as "% saturation"
- about 1/3 of binding sites are normally occupied

i) TIBC: Total Iron Binding Capacity

- measure of transferrin available to bind iron (a converse measurement of transferrin)
- plasma transporter; binds only a small amount of the total body iron
- utilitize to diagnose iron deficiency vs. anemia of chronic disease

j) Serum iron

- highly variable; NOT very good for diagnosing iron deficiency
- most useful in sorting out anemia of chronic disease vs Fe deficiency

k) Haptoglobin

- binds excess free hemoglobin in the serum
- particularly useful in the evaluation of hemolysis

l) Hemoglobin electrophoresis

- useful to evaluate hemoglobinopathies

m) Peripheral smear (Wright's stain): "the hematologists dictionary"

- acanthocytes: thorny spikes → rare; liver disease, cancer
- anisocytosis: variety of cell sizes → elevated RDW, suggest Fe++ deficiency
- basophilic stippling: thalassemia, sideroblastic anemia; lead poisons
- blister cells → G6PD deficiency
- burr cells: one or more spines & less spherical →suggest uremia
- elliptocytes : cigar shaped secondary to abnormal Hgb → suggest thalassemia
- Heinz bodies: precipitated denatured hemoglobin aggregates → G6PD, hemolytic anemias
- Howell Jolly bodies: nuclear remnants -- suggest asplenia, B12/Folate deficient
- macrocytosis -- large cells; defective maturation or stimulated erythropoesis suggests B12/Folate; alcohol; hypothyroidism OR shift cells → after Fe++ replacement therapy has begun
- microcytosis --small cells, → defective Hgb synthesis suggesting iron deficiency or thalassemia
- poikilocytosis: variety of cell shapes
- polychromatophilia: "more blue than usual" → reticulocytosis of any cause
- schistocytes: bites out of cells → suggest traumatic or hemolytic anemia;
- schizocytes (helmet cells): due to physical intravascular fragmentation
- sickle cells: obvious
- spherocytes: dense round cells from hemolysis → hereditary spherocytosis or auto immune anemias
- stomatocytes: abnormal K+/Na+ metabolism → alcohol, others
- target cells: excess membrane compared to Hgb → suggests hemoglobinopathy - impaired synthesis (Hgb S) and thalassemia; liver disease, iron deficinecy
- teardrop cells: shaped like teardrops → suggest myelofibrosis; homozygous β thalassemia

o) Bone marrow

Indications for Bone Marrow:

- Presence of nucleated rbc, immature leukocytes
- Pancytopenia or Absence of reticulocytes
- Estimation of iron stores
- Suspect sideroblastic anemia
- Moderate to severe anemia of ?? origin
- Combined nutritional anemias, chronic disease

III. CLASSIFICATION:

à BY PATHOPHYSIOLOGY

Decreased production - chronic disease (hypothyroid, renal disease); diet deficiency: inadequate iron intake or continued loss from bleed; marrow failure- secondary to tumor, drugs, fibrosis

Hemolysis - hemoglobinopathies, autoimmune disease

Increased loss - hemorrhage, trauma, neoplasm

à BY RED CELL MORPHOLOGY:

A. MICROCYTIC: MCV < 80

1. Thalassemia

History:

- 30% of African-Americans carry genes for α thalassemia
- 4 genes involved
- Beta thalasemia in patients of Med, Indian, Far East ancestry
- Hereditary microcytic anemia; abnormal synthesis of hemoglobin chain leads to overproduction of second chain→ aggregate, precipitate → hemolysis
- Dominant inheritance (thalassemia minor is the "carrier state" of the more severe (homozygous thalassemias)
- Normal life span of rbc

Laboratory:

- Microcytic anemia with Uniform RDW -- frequently normal (vs. iron deficiency anemia)
- Target cells are common--but NOT diagnostic!
- Hgb Electrophoresis confirms β thal; α-thalassemia diagnosis of exclusion by normal iron stores

2. Iron Deficiency

History:

- nutritional deficiency, poor absorption, excess loss, increased demand
  - humans have 3.5-5.0 gms of total body iron (most is in the rbcs)
  - Daily absorption of 1 mg/day is all that is required in men, women about double; requires consumption of 5-10 mg/d in men (7-20 mg/d in women); *however,* we only absorb 10% of available iron from the diet
  - In USA average diet contains 6 grams of iron/1000 calories
  - Men in USA rarely develop iron deficiency anemia from nutrition alone
  - Gastric acid facilitates iron absorption; gastrectomy, H2 blockers, Bilroth II decrease absorption;
  - Foods-especially vegetable fibers and phytates impair absorption
- 5 ml of blood contains 0.4 mg or iron (5 cc = 2 mg/day)

- GI blood loss most common cause in men; second to menstrual loss in women; repeated pregnancy is third; two ASA/day can lead to up to 4.5 cc/day EBL secondary to gastritis

Lab Diagnosis:

- Microcytosis, elevated RDW, decreased cell count, retic count low
- Failed response to iron therapy: HGB should increase by 2 g/dl by two weeks; normal Hgb in six weeks; retics should increase within days
- If no response: wrong DX, complicating illness, non-compliance, or poor iron absorption
- <u>LOW Ferritin; low transferrin confirms</u>

B. MACROCYTIC: MCV > 100 *(Macrocytosis ¹ Macrocytic Anemia)*

- 60% do not have associated anemia; BUT further eval <u>always</u> indicated
- Incidence: 1.7 - 3.6% of automated cell blood counts MCV >100
- Physicians often ignore isolated elevated MCV

Etiologies of Macrocytic Anemias:

- Alcoholism: 36% (marrow toxic, decrease folate absorption)
- B12 and folate deficiency: 21%
- Chemotherapy/other drugs therapy: 11%
  - ⇒ Retrovir: marrow toxic (detectable within 2 weeks)
  - ⇒ Phenobarb/phenytoin/alcohol/OCPs/Bactrim: deplete folate
  - ⇒ Cholchicine: depletes B12
- Other: hemolysis 7%, Liver disease 6%, hypothyroidism 2%
- Unknown: 12%

<u>Megaloblastic Anemia</u>

History

- Vegetarians → decrease B12 intake;
- Gastric disease/resection → malabsorption B12
- Elderly with poor dentition → decreased folate intake
- Medications

Physical Findings: nonspecific

- jaundice with liver disease; neurologic sensory deficits with B12

Laboratory:

- Low B12 or low folate
- Peripheral smear: hypersegmented neutrophils (>5 segments)
- Include TSH, LFTs → marrow if neg.

C. NORMOCYTIC: HYPOCHROMIC/NORMOCHROMIC/HYPERCHROMIC

1. Hemolysis Anemia and reticulocytosis in absence of blood loss

Characteristics:

- reduced red cell survival,
- retained iron stores in body;
- hyperactive bone marrow

Intravascular Hemolysis: red cells lyse in circulation
caused by trauma, complement fixation to red cells, exogenous toxins

Extravascular: ingestion of red cells by macrophages in spleen and liver
more common than intravascular

Physical: dark urine, jaundice, splenomegaly

Laboratory findings:

- anemia, elevated retic count, hemoglobinuria,
- peripheral smear → spherocytes, poikilocytosis, spur cells, target cells acanthocytes, sickle cell target cells;
- elevated LDH (from rbc's in intravascular hemolysis)
- low haptoglobin (binds hemoglobin for removal by hepatocytes)
- elevated unconjugated bilirubin (bound to albumin--not found in urine)

a. Acquired Hemolytic Anemias

Pathophysiology

- Splenomegaly causes "sequestration hemolysis"
- entrapment of normal red cells as they pass through enlarged spleen
- causes of splenomegaly→infiltrative diseases, systemic inflammatory disorders

i. Immune hemolytic anemias: 40-50% are idiopathic

- Abs or complement bind to rbc membrane (autoimmne, pregnancy, transfusions);
- think neoplasia, mycoplasma, mononucleosis, lupus, RA,
- drugs--aldomet, INH, sulfonamides quinidine penicillin
- Lab: *direct Coombs test confirms* → detects antibodies on the rbc

ii. Traumatic Hemolytic Anemias:

- Cardiac hemolysis: left sided cardiac lesions more often than right
- Abnormal Microcirculation (fibrin deposition)
- TTP, Hemolytic Uremic Syndrome, DIC
- Vessel wall abnormalities: malignant HTN, eclampsia, hemangiomas

iii. Direct Toxic Effect on RBCs

- Infections: malaria, clostridum welchii, Bartonella, Babesia
- Other: snake venom, burns, high temperatures

iv. Paroxysmal Nocturnal Hemoglobinuria

b. Hereditary Hemolytic Disorders (due to membrane, enzyme, or hemoglobin defects)
   i. Inherited Membrane Defects
      - Hereditary spherocytosis
      - Hereditary elliptocytosis, stomatocytosis
   ii. Defective hemoglobin synthesis
      a) alpha thalassemia: carrier state vs. affected state
         - heterozygous carrier state 30% asians, 20-30% in blacks
         - in affected state: microcytic, hypochromic; target cells, hemolysis
      b) β-thalassemia: Mediterranean, African Asia, south pacific, India
         - β-thalassemia major → transfusion dependent at 6 months of age
         - β-thalassemia intermedia → live to adult with hemolysis
         - β-thalassemia minor → no clinical anemia (but hgb 15% low,)
      c) Other Hemoglobinopathies: 400 variants
      d) Sickle cell trait/disease (8%/.15% of American blacks)

N.B.***hemoglobinemia, hemoglobinuria, hemosiderinuria → *massive rapid intravascular hemolysis* (transfusion reaction, PNH, G6PD deficiency, infection, burns); MUST BE URGENTLY TREATED

2. Anemias of Chronic Disease (Inflammatory, Infectious, Malignant)
   Often coexist with other causes for anemia
   Mechanisms:
   - Impaired release of iron from macrophages
   - Decreased erythropoietin production
   - Supression of erythropoiesis
   - Shorter erythrocyte survivial time

   Laboratory: diagnosis of exclusion
   - usually mild anemia, normochromic, normocytic (1/3 are hypochromic, microcytic)
   - Ferritin is usually normal → represents normal iron stores
   - Transferrin usually low (same as iron deficiency)

   Erythropoietin therapy has promise for treatment

III. TREATMENT

Treat underlying cause, if possible.

Iron Deficiency anemia: Treat with IRON! Follow retic count response. If no response → pt most likely non-compliant with FE therapy. In unusual cases they do not absorb the iron. May require parenteral FE.

In cases of bone marrow suppression secondary to malignancy or its treatments (eg. chemotherapy), Epogen, a synthetic hemopoetic stimulant can help boost response. **$$$$**
CASES:

References

Medical Clinics of North America; 89(6); May 1992. *A cornucopia of information.*

Geriatrics; 48(4):72-80; April 1993. *Common blood disorders: a primary care approach.*

JAMA; 259(16):2433-7; April 22, 1988. *A review of common anemias.*

Websites Links to Anemia Sites

http://www.ohsu.edu/cliniweb/handouts/anemia.html
A nice review of anemias in general from Oregon Health Sciences University.

http://www.uu.edu/CLASS/JMCGH/casestud/index.htm
Case studies in anemia by the same grad student.

http://misd-web1.ccf.org/ed/pated/database/docs/0012.htm
Patient education notes from the Cleveland Clinic.