

Update on (Approach to) Anemia

How to efficiently and accurately work up the anemic patient

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Anemia - Definition

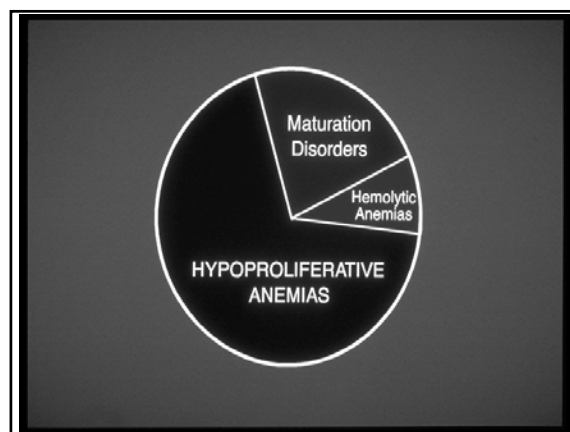
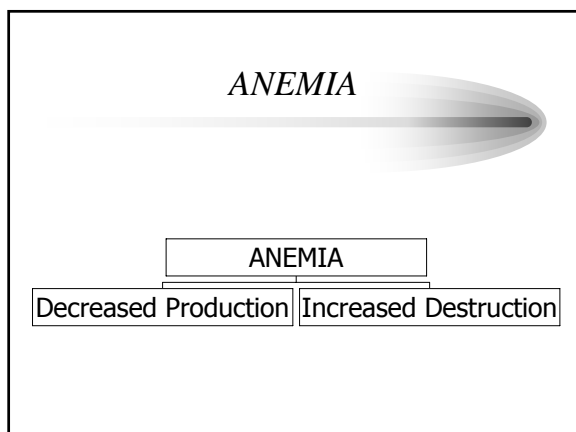
- Decrease in the number of circulating red blood cells
- Most common hematologic disorder by far
- Almost always a secondary disorder
- As such, critical for physicians to know how to evaluate/determine cause

Anemia - Causes

- Blood loss
- Decreased production of red blood cells (Marrow failure)
- Increased destruction of red blood cells
 - Hemolysis

Anemia Workup - Exaggerated

| | |
|-------------------------------------|------------------------------------|
| • Iron/TIBC/Ferritin | • Rheumatology screen |
| • Folate/B ₁₂ | • Acid hemolysis |
| • LDH/Bilirubin | • Osmotic fragility |
| • Haptoglobin/Urine for hemosiderin | • Rx iron/folate/B ₁₂ |
| • Coombs Test – Direct & indirect | • Type & Cross |
| • Hemoglobin electrophoresis | • Transfuse 2-4 units |
| | • GI Consult |
| | • Hematology Consult – Bone Marrow |

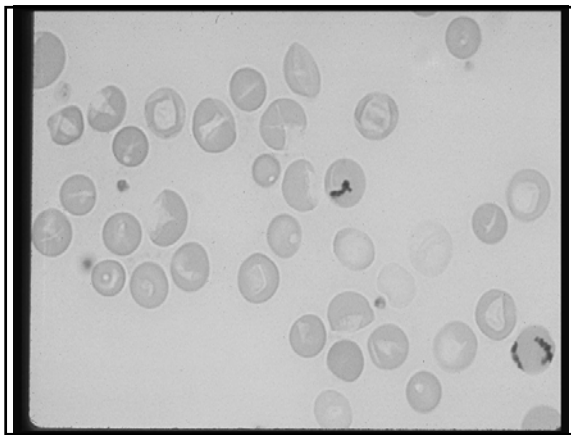


Anemia – Basic Workup

- History and Exam
- Reticulocyte count
 - Blood film
 - MCV
 - Ferritin
- WBC, diff, platelets

Anemia Workup - 1st Test

RETICULOCYTE COUNT!!!



Reticulocyte Count - Absolute Value

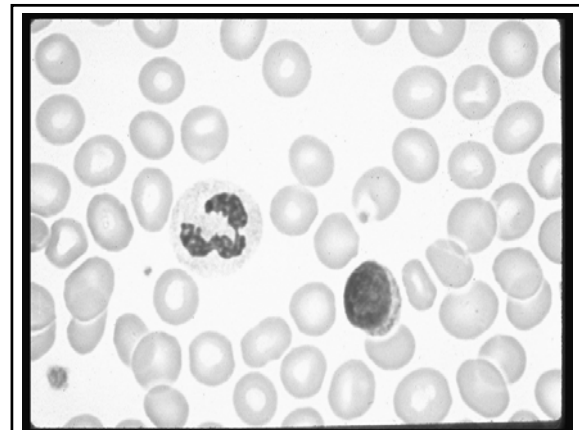
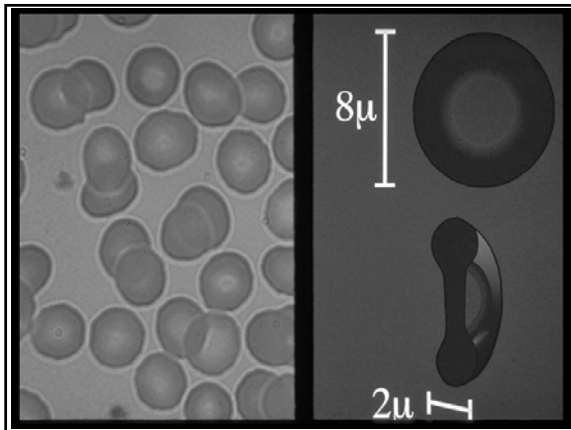
- = Retic % x RBC Count
 - eg $0.01 \times 5 \times 10^{11}/l = 5 \times 10^9/l$
- Normal up to $1.2 \times 10^{11}/l$ (120,000/ μ l)
- More accurate way to assess body's response to anemia

Anemia Workup

- If retic count is elevated, following tests not needed:
 - Iron/Iron Binding Capacity/Ferritin
 - Folate/Vitamin B₁₂
 - Acid Hemolysis
 - GI Consult
 - Bone Marrow

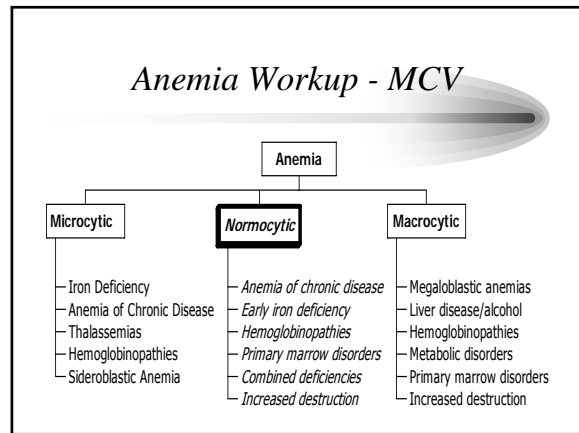
Anemia - Peripheral Blood Smear Findings

- Look for size and shape of RBC's - esp for variability in sizes & shapes
- Is there polychromasia present? (Often implies reticulocytosis)
- Is there a dimorphic population of RBCs?
- Are there platelet and WBC abnormalities?



Mean Corpuscular Volume

| | <i>MCV</i> |
|------------|------------|
| Macrocytic | >100 fl |
| Normocytic | 80-100 fl |
| Microcytic | < 80 fl |



- Anemia – Normocytic (MCV 80-100)*
- Most commonly caused by anemia of chronic disease
 - Early iron deficiency often causes normocytic anemia as well
 - Anemia of chronic investigation – particular hazard of ICU patients
 - Combined deficiencies

- Anemia of Chronic Disease*
- Common
 - Develops over 1 to 2 months
 - Non-progressive
 - Usually mild to moderate
 - but hematocrit < 0.20 occasionally
 - 30% mildly microcytic
 - WBC, platelets normal or increased

Anemia of Chronic Disease - Pathophysiology

- Cytokine effects (eg, IL-1, TNF)
- DNA & RNA iron-response elements
- ↓ erythropoietin responsiveness (& production)
- ↓ transferrin synthesis
- ↓ Fe mobilization from macrophages
 - ↓ Fe re-utilization in erythropoiesis
 - ↓ serum Fe despite adequate stores
 - ↑ serum ferritin
- Reticulocytopenia
- Anemia

Effects of Interleukin-1 (IL-1)

Stimulates

Inhibits

- | | |
|---|---|
| <ul style="list-style-type: none"> ▪ fever ▪ granulopoiesis ▪ thrombopoiesis ▪ synthesis of: <ul style="list-style-type: none"> ▪ ferritin ▪ Ig ▪ fibrinogen, VIII ▪ CRP ▪ IL-2, IL-6 | <ul style="list-style-type: none"> ▪ erythropoiesis ▪ synthesis of: <ul style="list-style-type: none"> ▪ transferrin ▪ albumin |
|---|---|

ANEMIA OF CHRONIC DISEASE - Causes

- Thyroid disease
- Collagen Vascular Disease
 - Rheumatoid Arthritis
 - Systemic Lupus Erythematosus
 - Polymyositis
 - Polyarteritis Nodosa
- Inflammatory Bowel Disease
 - Ulcerative Colitis
 - Crohn's Disease
- Malignancy
- Chronic Infectious Diseases
 - Osteomyelitis
 - Tuberculosis
- Familial Mediterranean Fever
- Renal Failure

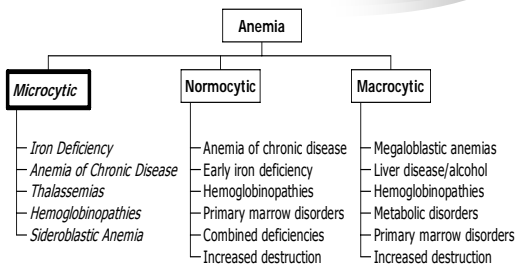
Marrow Failure

Normocytic Anemia (MCV 80-100 fl)

| Type of anemia | Blood film | Ferritin | Fe | TIBC | Fe stores |
|---------------------|--------------------------------|----------|----|------|------------------|
| Chronic disease* | Normochromic, normocytic | Nl or ↑ | ↓ | ↓ | Nl or ↑, clumped |
| Early Fe deficiency | Mild anisocytosis, hypochromia | Nl or ↓ | ↓ | ↑ | absent |

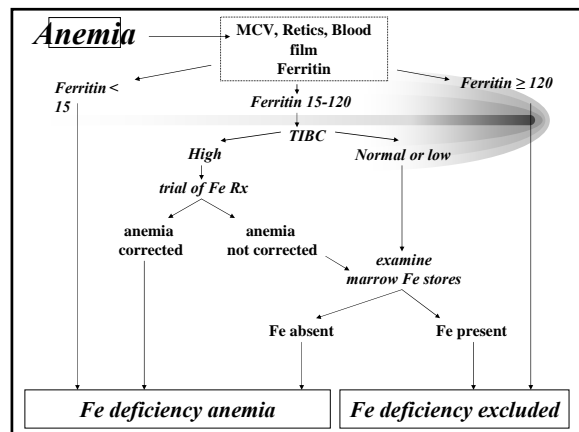
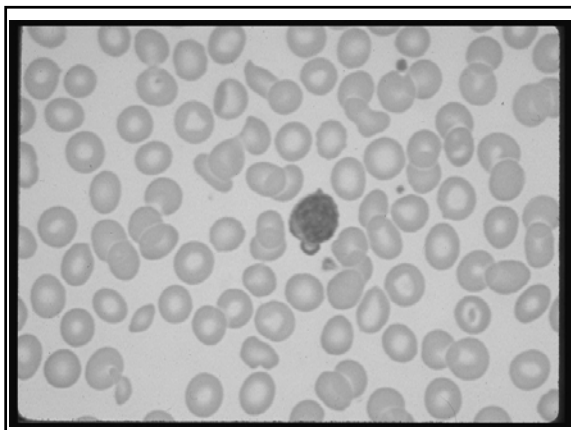
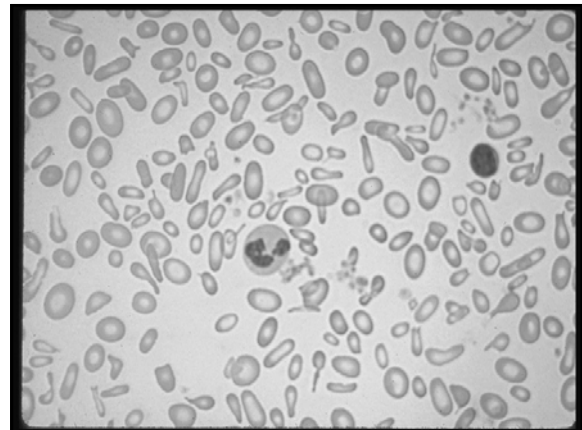
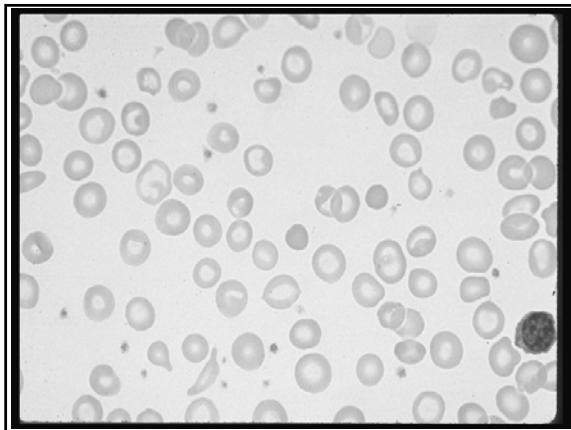
*including anemia due to renal disease and AIDS

Anemia Workup - MCV



ANEMIA - Microcytic (MCV < 80)

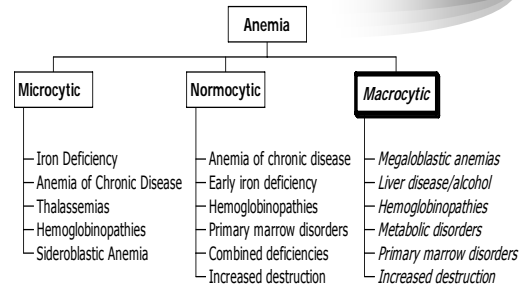
- Iron Deficiency - High RDW (Red cell distribution width)
- Thalassemia minor - Normal RDW
- Rare
 - Sideroblastic anemia
 - Metal poisoning (esp lead, aluminum)
 - Occasional hemoglobinopathies
 - Thalassemia major



Soluble Transferrin Receptor

- Measure of ferrokinetic activity
- Elevated in iron deficiency
- Not usually elevated in anemia of chronic inflammation (not an acute phase reactant)
- Still not widely available
- Expensive
- May replace iron binding capacity &/or ferritin

Anemia Workup - MCV



Anemia - Macrocytic (MCV > 100)

- If MCV 100-110 fl, must look for other causes of macrocytosis
- If MCV > 110 fl, almost always folate or cobalamin deficiency

Macrocytosis (MCV > 100 fl)

- Common
 - Drugs (cytotoxics, immunosuppressants, AZT, anticonvulsants)
 - Alcohol
 - Liver disease
 - Reticulocytosis
 - B₁₂/folate deficiency
 - Myelodysplastic syndrome
 - Marrow infiltration (malignancy, fibrosis)
- Less common
 - Aplasia
- 'Artifactual'
 - Cold agglutinins
 - Hyperglycemia
 - Hyperleukocytosis

Macrocytosis of Alcoholism

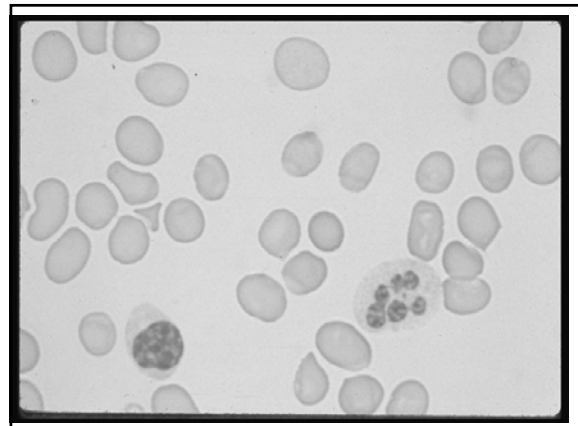
- 25-96% of alcoholics
- MCV elevation usually slight (100-110 fl)
- Minimal or no anemia
- Macrocytes round (not oval)
- Neutrophil hypersegmentation absent
- Folate stores normal

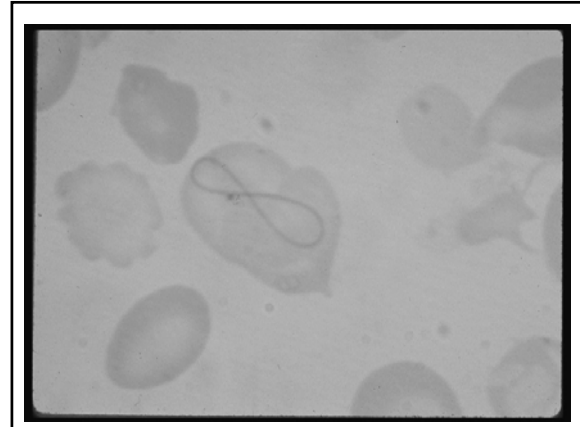
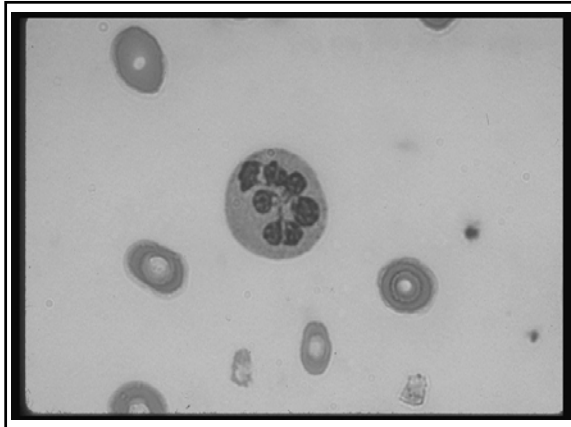
Megaloblastic Hematopoiesis

- Marrow failure due to: disrupted DNA synthesis & ineffective hematopoiesis
- Giant precursors and nuclear:cytoplasmic dyssynchrony in marrow
- Neutrophil hypersegmentation & macroovalocytes in blood
- Anemia (and often leukopenia & thrombocytopenia)
- Almost always due to Cbl or folate deficiency

Evolving Cobalamin Deficiency

- Usual sequence:
 - Serum Cobalamin falls
 - Serum methylmalonic acid & homocysteine rise
 - MCV rises within the normal range, with hypersegmentation of neutrophils
 - MCV rises above normal
 - Anemia and/or neuropathy
 - Symptoms





'Dimorphic' Anemias

- Folate & Fe deficiency (eg, pregnancy, alcoholism)
- B₁₂ & Fe deficiency (eg, pernicious anemia with atrophic gastritis)
- Thalassemia minor & B₁₂ or folate deficiency
- Fe deficiency & hemolysis (eg, prosthetic valve)
- Folate deficiency & hemolysis (eg, HgbSS disease)
- Blood smear critical to assess these

Hemolytic Anemia

- Anemia of increased destruction
 - Normochromic, normochromic anemia
 - Shortened RBC survival
 - Reticulocytosis - Response to increased RBC destruction

Tests Used to Diagnose Hemolysis

- Reticulocyte count (combined with serial Hb)
- Haptoglobin
- Urine hemosiderin
- Also helpful:
 - Serum bilirubin
 - Serum LDH
 - Hemoglobinuria

Findings Consistent with Hemolysis

| | |
|--------------------------------|-----------|
| Serum unconjugated bilirubin | Increased |
| Serum LDH (and LDH1:LDH2) | Increased |
| Serum haptoglobin | Decreased |
| Urine hemoglobin | Present |
| Urine hemosiderin | Present |
| Urine urobilinogen | Increased |
| Cr ⁵¹ -RBC lifespan | Decreased |
| Reticulocyte count | Increased |

(problems with sensitivity and specificity; none define cause)

Blood morphology in hemolytic anemias

| | |
|--------------------|--|
| Sickle cells | Sickle cell anemia |
| Hb crystals | Hb CC disease |
| Fragments, helmets | Microangiopathic hemolysis |
| Microspherocytes | Hereditary spherocytosis Immune hemolysis |
| Elliptocytes | Hereditary elliptocytosis |

N.B., hemolysis is not excluded by a normal blood smear.

Tests to define the cause of hemolysis

- Hemoglobin electrophoresis
- Hemoglobin A₂ (beta-thalassemia trait)
- RBC enzymes (G6PD, PK, etc)
- Direct & indirect antiglobulin tests (immune)
- Cold agglutinins
- Osmotic fragility (spherocytosis)
- Acid hemolysis test (PNH)
- Clotting profile (DIC)

NB: These tests do not demonstrate the presence of hemolysis

Anemia Summary

- Check reticulocyte count 1st
 - If elevated, look for causes of increased destruction or bleeding
 - If normal or decreased, look for causes of marrow failure
 - Workup for marrow failure tailored by MCV, RDW, and peripheral blood smear
 - If low, iron problems or globin problems
 - If high, megaloblastic or DNA problems
 - If normal, need to look for combined anemias