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 internist to know how to evaluate/determine cause

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Anemia - Causes

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

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Anemia Workup - Exaggerated

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

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ANEMIA

ANEMIA

Decreased Production | Increased Destruction

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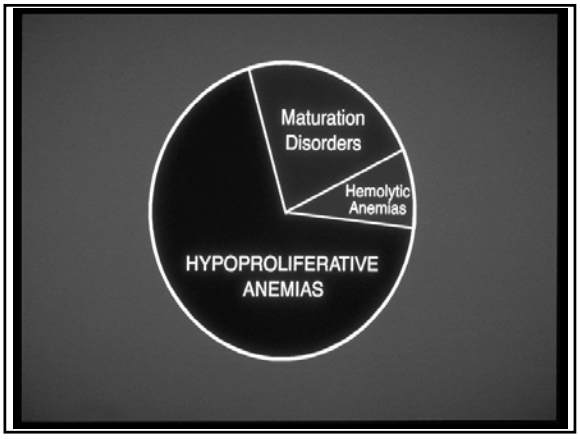

Anemia

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

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Anemia Workup - 1st Test

RETICULOCYTE COUNT

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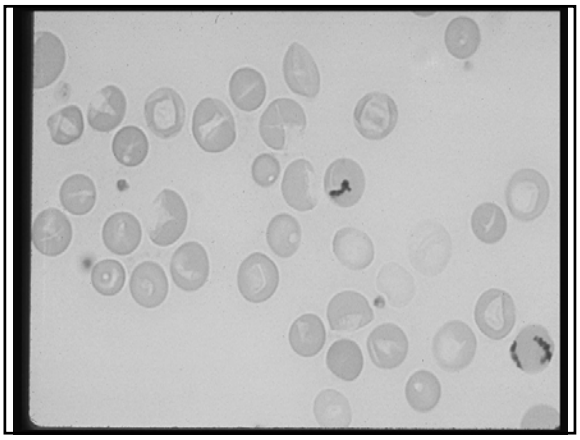

Reticulocyte Count - Absolute Value

- = Retic % x RBC Count
  - eg 0.01 x $5x10^{12}$/l = $5x\ 10^{10}$/l
- Normal up to $1.2x10^{11}$/l (120,000/µl)
- More accurate way to assess body's response to anemia

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Anemia Workup

- If retic count is elevated, following tests not needed:
  - Iron/Iron Binding Capacity/Ferritin
  - Folate/Vitamin B_{12}
  - Acid Hemolysis
  - GI Consult
  - Bone Marrow

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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?

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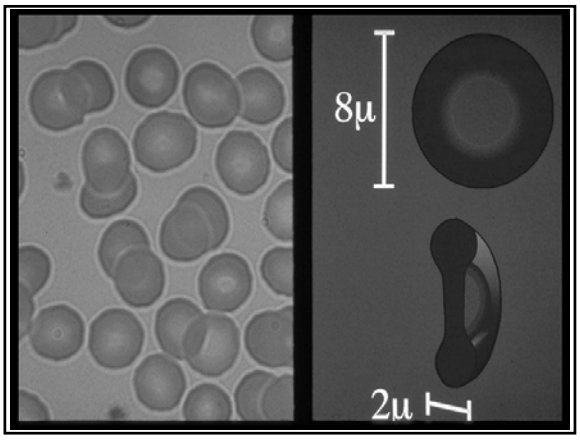
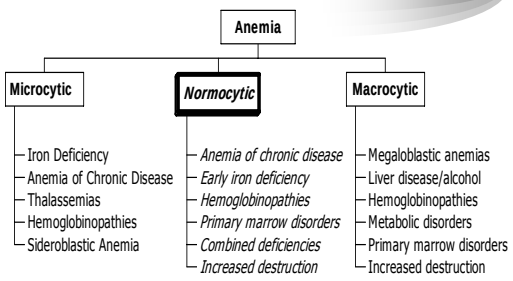


Anemia Workup - MCV



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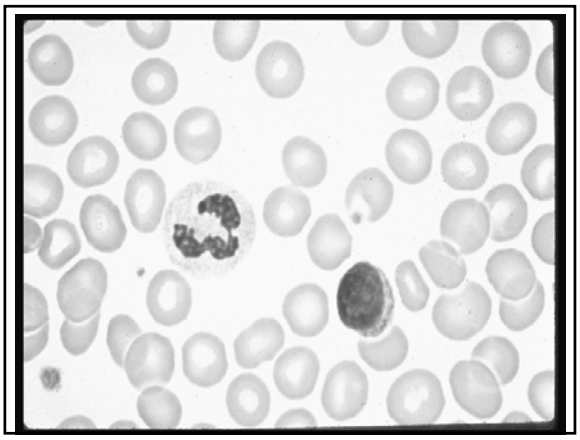

Anemia – Normocytic (MCV 80-100)

- 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

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Mean Corpuscular Volume

	MCV
Macrocytic	>100 fl
Normocytic	80-100 fl
Microcytic	< 80 fl

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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

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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

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Effects of Interleukin-1 (IL-1)

Stimulates	*Inhibits*

▪ fever
▪ granulopoiesis
▪ thrombopoiesis
▪ synthesis of:
  ▪ ferritin
  ▪ Ig
  ▪ fibrinogen, VIII
  ▪ CRP
  ▪ IL-2, IL-6
	▪ erythropoiesis
	▪ synthesis of:
	  ▪ transferrin
	  ▪ albumin

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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

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Marrow Failure
Normocytic Anemia (MCV 80-100 fl)

Type of anemia	*Blood film*	*Ferritin*	*Fe*	*TIBC*	*Marrow 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

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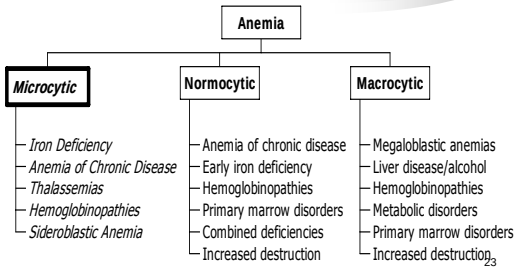
Anemia Workup - MCV



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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

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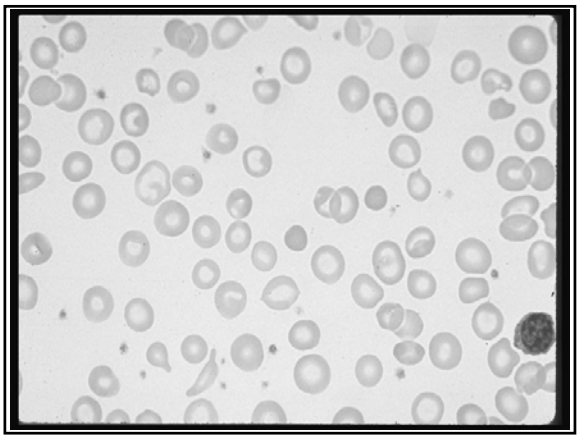
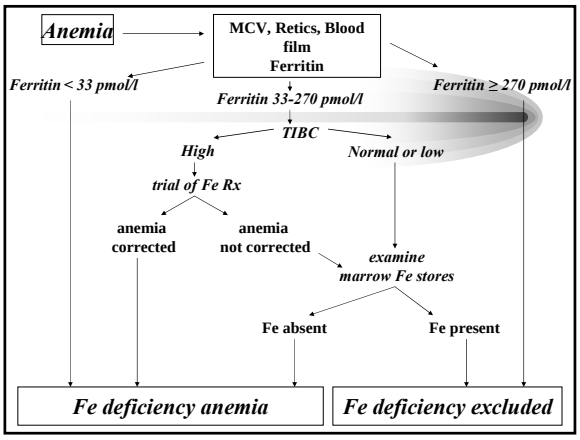
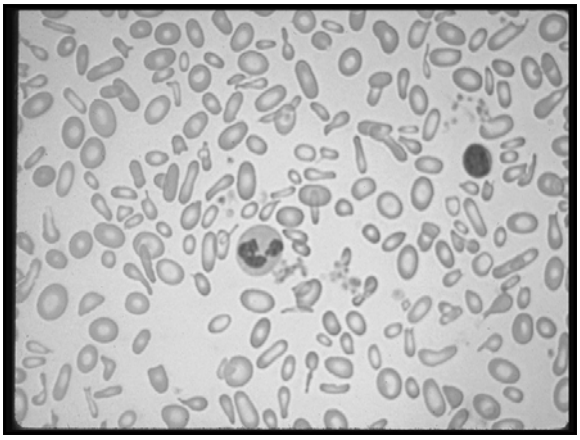
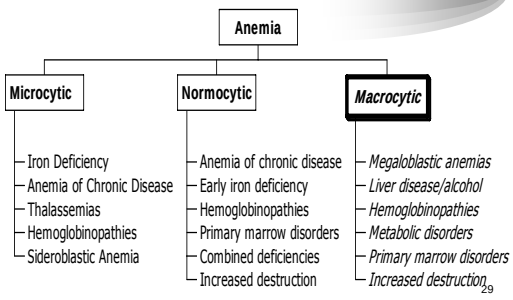






Anemia Workup - MCV



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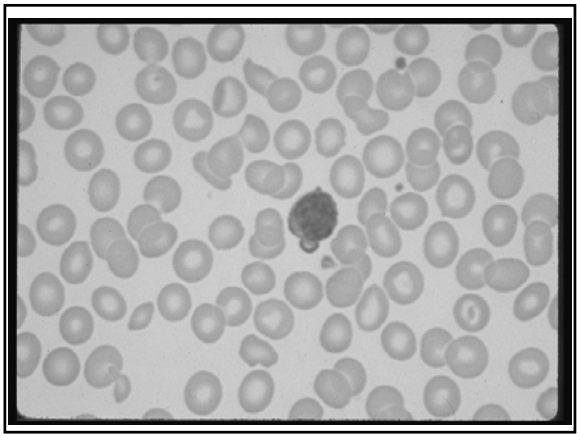

Anemia - Macrocytic (MCV > 100)

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

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Macrocytosis (MCV > 100 fl)

- Common
  - Drugs (cytotoxics, immunosuppressants, AZT, anticonvulsants)
  - Alcohol
  - Liver disease
  - Reticulocytosis
  - B_{12}/folate deficiency
  - Myelodysplastic syndrome
  - Marrow infiltration (malignancy, fibrosis)
- Less common
  - Aplasia
- 'Artifactual'
  - Cold agglutinins
  - Hyperglycemia
  - Hyperleukocytosis

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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

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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

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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

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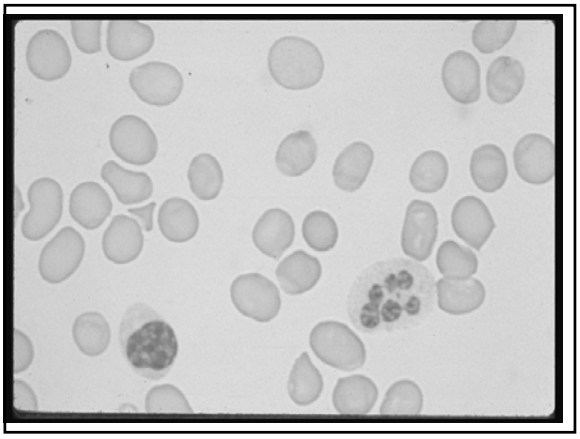

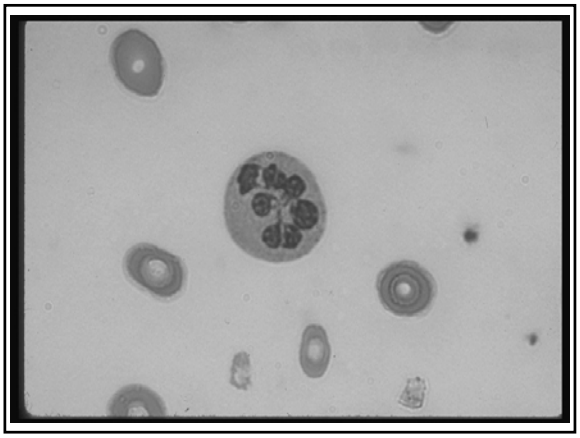

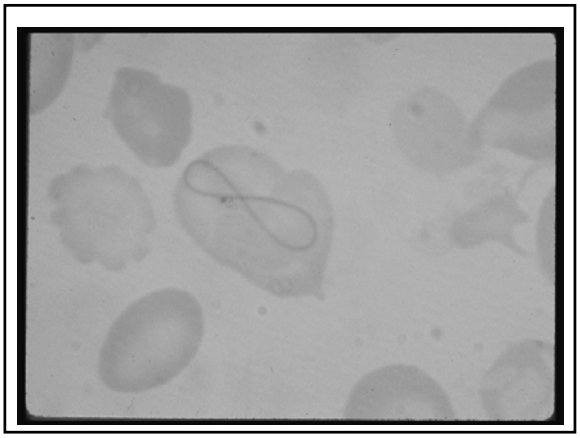

Tests Used to Diagnose Hemolysis

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

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'Dimorphic' Anemias

- Folate & Fe deficiency (*eg*, pregnancy, alcoholism)
- B_{12} & Fe deficiency (*eg*, pernicious anemia with atrophic gastritis)
- Thalassemia minor & B_{12} or folate deficiency
- Fe deficiency & hemolysis (*eg*, prosthetic valve)
- Folate deficiency & hemolysis (*eg*, HgbSS disease)
- Blood smear critical to assess these

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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)

Hemolytic Anemia

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

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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.

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Tests to define the cause of hemolysis

- Hemoglobin electrophoresis
- Hemoglobin A_2 (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

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Anemia – Clinical Consequences

- General
  - Slowly developing anemia is well tolerated
  - Rapidly developing anemia is not well tolerated
  - No specific hemoglobin level necessary for optimized oxygen delivery to tissues
  - People with congenital abnormal hemoglobins tolerate much lower levels than most

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Anemia – Clinical Consequences 2

- Oxygen delivery increases linearly with increasing hemoglobin
- Blood viscosity increases exponentially, & flow decreases exponentially, with increasing hemoglobin
- Optimum oxygen delivery occurs with hemoglobin level c. 150 grams/liter
- Significant decreases in oxygen delivery don't happen until hemoglobin is > 180 grams/liter

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Anemia – Clinical Consequences 3

- Degree of anemia often a marker for degree of illness
- Below hemoglobin 100 grams/l, most will have some symptoms of fatigue
- Pharmacologic doses of erythropoietin clearly will improve hemoglobin in most with anemia of chronic disease

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Anemia – Clinical Consequences 4

- Other vitamins/minerals need to be repleted for erythropoietin to work
- Not clear that increasing hemoglobin level increases survival or prevents other complications of underlying disease

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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

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Anemia – Summary 2

- If vitamins/minerals replete & patient still anemic, erythropoietin can be used to raise hemoglobin level
- ? If raising hemoglobin level alters underlying disease process

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