Update on (Approach to) Anemia

How to efficiently and accurately work up the anemic patient

David L. Diuguid, MD
Associate Professor of Clinical Medicine & Clinical Pathology
College of Physicians & Surgeons of Columbia University

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
- Folate/B12
- LDH/Bilirubin
- Haptoglobin/Urine for hemosiderin
- Coombs Test – Direct & indirect
- Hemoglobin electrophoresis
- Rheumatology screen
- Acid hemolysis
- Osmotic fragility
- Rx iron/folate/B12
- Type & Cross
- Transfuse 2-4 units
- GI Consult
- Hematology Consult – Bone Marrow

ANEMIA

Decreased Production | Increased Destruction

Maturational Disorders
Hemolytic Anemias
Hypoproliferative Anemias
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 x 5x10^11/l = 5x10^9/l
- Normal up to 1.2x10^11/l (120,000/μl)
- 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**

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

**Anemia Workup - MCV**

- Anemia
  - Microcytic
  - Normocytic
  - Macrocytic
    - Iron Deficiency
    - Anemia of Chronic Disease
    - Thalassemias
    - Hemoglobinopathies
    - Sideroblastic Anemia
    - Anemia of chronic disease
    - Early iron deficiency
    - Hemoglobinopathies
    - Primary marrow disorders
    - Combined deficiencies
    - Increased destruction

**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 (e.g., 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)

<table>
<thead>
<tr>
<th>Stimulates</th>
<th>Inhibits</th>
</tr>
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<tbody>
<tr>
<td>fever</td>
<td>erythropoiesis</td>
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<tr>
<td>granulopoiesis</td>
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<td>thrombopoiesis</td>
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<tr>
<td>synthesis of:</td>
<td>synthesis of:</td>
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<tr>
<td>ferritin</td>
<td>transferrin</td>
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<tr>
<td>Ig</td>
<td>albumin</td>
</tr>
<tr>
<td>fibrinogen, VIII</td>
<td></td>
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<tr>
<td>CRP</td>
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<tr>
<td>IL-2, IL-6</td>
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</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Type of anemia</th>
<th>Blood film</th>
<th>Ferritin</th>
<th>Fe</th>
<th>TIBC</th>
<th>Fe stores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Disease</td>
<td>Normocytic</td>
<td>M or ↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Early Fe deficiency</td>
<td>Mild anemia</td>
<td>M or ↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

*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
**Update on (Approach to) Anemia**

**October 2, 2003 10:00 am**

**MCV, Retics, Blood film**
- Ferritin

Ferritin < 15
  - Ferritin 15-120
    - TIBC
    - trial of Fe Rx

anemia corrected
anemia not corrected

examine marrow Fe stores

- Fe absent
- Fe present

Fe deficiency anemia
Fe deficiency excluded

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**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

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**Anemia Workup - MCV**

- Microcytic
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  - Sideroblastic Anemia

- Normocytic
  - Anemia of chronic disease
  - Early iron deficiency
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  - Primary marrow disorders
  - Combined deficiencies
  - Increased destruction

- Macrocytic
  - Megaloblastic anemias
  - Liver disease/alcohol
  - Hemoglobinopathies
  - Metabolic disorders
  - Primary marrow disorders
  - Increased destruction
**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
  - Reticuloctyosis
  - B12/folate deficiency
  - Myelodysplastic syndrome
  - Marrow infiltration (malignancy, fibrosis)
- Less common
  - Aplasia
  - ‘Artifactual’
    - Cold agglutinins
    - Hyperglycemia
    - Hyperleukocytosis

**Macrocystosis 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 (e.g., pregnancy, alcoholism)
- B₁₂ & Fe deficiency (e.g., pernicious anemia with atrophic gastritis)
- Thalassemia minor & B₁₂ or folate deficiency
- Fe deficiency & hemolysis (e.g., prosthetic valve)
- Folate deficiency & hemolysis (e.g., 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
- Cr²⁵-RBC lifespan: Decreased
- Reticulocyte count: Increased

(problems with sensitivity and specificity; none define cause)
**Blood morphology in hemolytic anemias**

<table>
<thead>
<tr>
<th>Sickle cells</th>
<th>Sickle cell anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb crystals</td>
<td>Hb CC disease</td>
</tr>
<tr>
<td>Fragments, helmets</td>
<td>Microangiopathic hemolysis</td>
</tr>
<tr>
<td>Microspherocytes</td>
<td>Hereditary spherocytosis</td>
</tr>
<tr>
<td>Elliptocytes</td>
<td>Hereditary elliptocytosis</td>
</tr>
</tbody>
</table>

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