Update on (Approach to) Anemia

How to efficiently and accurately work up the anemic patient

David L. Disquid, MD
Associate Professor of Clinical Medicine
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 internist to know how to evaluate/determine cause

Anemia Workup - Exaggerated

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

Anemia - Causes

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

ANEMIA

Decreased Production | Increased Destruction

HYPOPROLIFERATIVE ANEMIAS

Maturation Disorders

Hemolytic Anemias
Anemia

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

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

Anemia Workup - 1st Test

RETICULOCYTE COUNT

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?
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October 2, 2003 10:00 am

Mean Corpuscular Volume

<table>
<thead>
<tr>
<th>Type</th>
<th>MCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrocytic</td>
<td>&gt;100 fl</td>
</tr>
<tr>
<td>Normocytic</td>
<td>80-100 fl</td>
</tr>
<tr>
<td>Microcytic</td>
<td>&lt; 80 fl</td>
</tr>
</tbody>
</table>

Anemia Workup - MCV

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)**

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

**ANEMIA OF CHRONIC DISEASE - Causes**

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

**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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**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>Marrow Fe stores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic disease*</td>
<td>Normochromic, normocytic</td>
<td>Ni or ↑</td>
<td>↓</td>
<td>↓</td>
<td>Ni or ↑, clumped</td>
</tr>
<tr>
<td>Early Fe deficiency</td>
<td>Mild anisocytosis, hypochromia</td>
<td>Ni or ↓</td>
<td>↓</td>
<td>↑</td>
<td>absent</td>
</tr>
</tbody>
</table>

*including anemia due to renal disease and AIDS*
**Update on (Approach to) Anemia**

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

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**Anemia Workup - MCV**

- **Microcytic**
  - Iron Deficiency
  - Anemia of Chronic Disease
  - Thalassemias
  - Hemoglobinopathies
  - Sideroblastic Anemia

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

- **Macrocytic**
  - Megaloblastic anemias
  - Liver disease/alcohol
  - Hemoglobinopathies
  - Metabolic disorders
  - Primary marrow disorders
  - Increased destruction

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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
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
- Macrocyes 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
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### ‘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

<table>
<thead>
<tr>
<th>Test</th>
<th>Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum unconjugated bilirubin</td>
<td>Increased</td>
</tr>
<tr>
<td>Serum LDH (and LDH1:LDH2)</td>
<td>Increased</td>
</tr>
<tr>
<td>Serum haptoglobin</td>
<td>Decreased</td>
</tr>
<tr>
<td>Urine hemoglobin</td>
<td>Present</td>
</tr>
<tr>
<td>Urine hemosiderin</td>
<td>Present</td>
</tr>
<tr>
<td>Urine urobilinogen</td>
<td>Increased</td>
</tr>
<tr>
<td>Cr⁵¹-RBC lifespan</td>
<td>Decreased</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>Increased</td>
</tr>
</tbody>
</table>

(problems with sensitivity and specificity; none define cause)

### Blood morphology in hemolytic anemias

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cells</td>
<td>Sickle cell anemia</td>
</tr>
<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>Immune hemolysis</td>
<td></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 – 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

- 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

- 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

- 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

Anemia – Clinical Consequences 3

Anemia – Clinical Consequences 4

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
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