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
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
- 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

HYPOPROLIFERATIVE ANEMIAS

- Maturation Disorders
- Hemolytic Anemias
Anemia

- 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^{12}/l = 5x10^{10}/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 $B_{12}$
  - 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

<table>
<thead>
<tr>
<th>MCV</th>
<th></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**
  - **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
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**
- fever
- granulopoiesis
- thrombopoiesis
- synthesis of:
  - ferritin
  - Ig
  - fibrinogen, VIII
  - CRP
  - IL-2, IL-6

**Inhibits**
- erythropoiesis
- synthesis of:
  - 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)

<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>Nl or ↑ ↓ ↓</td>
<td>Nl or ↑, clumped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Fe deficiency</td>
<td>Mild anisocytosis, hypochromia</td>
<td>Nl or ↓ ↓ ↑</td>
<td>absent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*including anemia due to renal disease and AIDS
**Anemia Workup - MCV**

**Microcytic**
- Iron Deficiency
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- Hemoglobinopathies
- Sideroblastic Anemia

**Normocytic**
- Anemia of chronic disease
- Early iron deficiency
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- Combined deficiencies
- Increased destruction

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

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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
Anemia

Fe deficiency anemia

Fe deficiency excluded

MCV, Retics, Blood film
Ferritin

Ferritin < 33 pmol/l
Ferritin ≥ 270 pmol/l

TIBC

High

Normal or low

trial of Fe Rx

anemia not corrected

examine marrow Fe stores

Fe absent

Fe present

anemia corrected

Ferritin 33-270 pmol/l

Fe deficiency excluded
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
Macrocytosis (MCV > 100 fl)

- **Common**
  - Drugs (cytotoxics, immnosuppressants, 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)
- $B_{12}$ & 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
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**

<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 – 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
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

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
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

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