ANEMIA: Evaluation and Management

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April 2015 Refresher Course
Objectives

- Generate a differential diagnosis for anemia based on the results of a CBC.
- Use a three part strategy to narrow the differential diagnosis of anemia.
- Describe common causes of anemia in the U.S.
- Describe a reasonable initial approach to ordering tests and evaluating patients newly diagnosed with anemia.
- Determine when to treat, refer, and monitor patients with common causes of anemia.
Anemia: defined

- Reduced red blood cell mass or reduced number of circulating red blood cells.
- On a complete blood count:
  - Low RBC count, low hemoglobin, low hematocrit
- Clinical definitions vary, but generally:
  - Women: Hgb < 12 g/dl (WHO definition)
  - Men: Hgb < 13 g/dl (WHO definition)
  - African-Americans have Hgb levels 0.5 – 1 g/dl lower on average and may require an alternative definition
Anemia: defined by consequences

- When controlled for disease and severity of illness, anemia has been associated with an increased risk of death.

- Anemia is strongly correlated with increased rates of death and mobility disability in older community-dwelling whites (but not blacks).

- In the setting of renal failure and chemotherapy, anemia is associated with decreased QOL and tx of anemia is associated with improved QOL.
Anemia: defined by consequences

- Look on the bright side... Oxygen delivery to peripheral tissues can be maintained at hemoglobin levels of 8-9 g/dL.
- Falling hemoglobin:
  - $\geq 9$ g/dL - no symptoms
  - 7-8 g/dL - dyspnea on exertion
  - 5-6 g/dL - profound fatigue
  - 3-4 g/dL - dyspnea at rest
  - 2 g/dL - heart failure
But...

...anemia is common and so is fatigue.

For example, a study by Elnicki (Am J Med 1992) found that one in 52 patients presenting to a primary care clinic for fatigue had anemia.
What’s the first thing you need?

- If your answer was “a CBC, of course!” then you are correct!

- Then, you can use an algorithm based on the other cell counts and indices to steer you in the right direction.

Let’s get it started…
Algorithm for microcytic anemia

1. Microcytic anemia
   - Check serum ferritin
     - Low
       - Iron deficiency anemia
     - Acquired microcytosis
       - Consider anemia of chronic disease
         - Usual causes
           - Temporal arteritis
           - Rheumatoid arthritis
           - Chronic inflammation
           - Chronic infection
         - Unusual causes
           - Hodgkin lymphoma
           - Renal cell carcinoma
           - Castleman disease
           - Myelofibrosis
     - Normal or elevated
       - Chronic microcytosis
         - Consider thalassemia
         - Hemoglobin electrophoresis
         - Hematology consultation
Algorithm for normocytic anemia

1. Reticulocytes
   - Increased
   - Not increased
   - Increased
   - Hemolysis or blood loss

2. Other cytopenias?
   - Abnormal leukocytes
   - Yes
   - Bone marrow evaluation for aplastic anemia, marrow infiltration, myelodysplastic syndrome, etc.
   - No
   - Evaluate clinical history

3. Chronic illness
   - Increased ferritin, decreased serum iron, decreased TIBC
   - Anemia of chronic disease

4. Renal dysfunction
   - Anemia of renal failure

5. Antecedent viral illness, drug exposure, lymphoproliferative disorder, mediastinal mass
   - Bone marrow biopsy to evaluate for red cell aplasia

Lumper or splitter?
Algorithm for macrocytic anemia

Mean corpuscular volume > 100 fl, order peripheral smear, vitamin B₁₂ level, and reticulocyte count.

Is peripheral blood smear abnormal?

No (no megaloblastic features)
- Consider alcohol-related, drug-related, thyroid-related, and liver disease pathologies, and consider checking liver function tests and thyroid-stimulating hormone levels.

Yes (megaloblastic features)
- Reticulocyte count > 2 percent?
  - No
    - Review vitamin B₁₂ level.
  - Yes
    - Suspect hemolysis and work-up for hemolytic anemia.

Vitamin B₁₂ level is < 100 pg per mL (74 pmol per L)
- Check MMA and homocysteine levels.
  - MMA and homocysteine levels are elevated
    - Vitamin B₁₂ deficiency
      - Treat with oral vitamin B₁₂.
  - MMA level is elevated and homocysteine level is normal
    - Consider further evaluation with bone marrow biopsy.
  - MMA and homocysteine levels are normal
    - MMA level is normal and homocysteine level is elevated
      - Folic acid deficiency
        - Treat with folic acid.

Vitamin B₁₂ level is 100 to 400 pg per mL (295 pmol per L)
- Check MMA and homocysteine levels.
  - MMA level is normal and homocysteine level is normal
    - Folic acid deficiency
      - Treat with folic acid.

Vitamin B₁₂ level is > 400 pg per mL; order RBC folate level
- RBC folate level is low
  - Consider further evaluation with bone marrow biopsy.
- RBC folate level is normal
  - Consider further evaluation with bone marrow biopsy.

Why not get the folate here?
What else do you want?

…and don’t forget the retic count!
Tips on getting a smear

- Not automatic. May need to request it.
- Helpful in:
  - Suspected hemolytic anemia
  - WBC disorders (i.e., suspected leukemia)
  - Platelet disorders
- Not needed to diagnose iron deficiency anemia.
- Not helpful in differentiating iron deficiency anemia from anemia of chronic disease/inflammation.

*Note: retic count, WBC differential, & smear are not routine w/ CBC at UIHC.*
### Findings on peripheral blood smear and their associated disease states

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<th>Findings</th>
<th>autoimmune hemolytic anemia</th>
<th>hereditary spherocytosis</th>
<th>acute leukemia</th>
<th>chronic leukemia</th>
<th>iron deficiency anemia</th>
<th>anemia of chronic disease</th>
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So, you know the patient is anemic. You have the CBC, smear and retic count. Now what?
Three part strategy to evaluating anemia

Symptom of an underlying disease

Size/shape/characteristics

Production v. removal
Looking at the CBC

1. Is it just anemia or are other cell lines affected?
2. How big are the red cells (measured by MCV)?
3. Is there anything else to glean from the other indices?
4. Refer to those algorithms to get you started.
Reticulocytosis

- In a normal person, retics ~ 1% of RBCs or number about 50,000/mcL.
- Under conditions of increased RBC loss, retics may increase by a factor of 5 (~250,000/mcL).
- Note: look at the absolute number of retics and as a percent of RBCs.
  - Anemic patients with 1% retics are *under-producing*.
  - Anemic patients with 50,000 retics/mcL are *under-producing*.
Reticulocytosis

Reticulocyte production index (RPI)

- Corrected for anemia and increased reticulocyte life-span that occurs in anemic patients
- RPI: normal value is 1, appropriate response to anemia is 2
- \[ RPI = \text{retic} \% \times \left( \frac{\text{HCT}}{45} \right) \times \left( \frac{1}{\text{RMT}} \right) \]
  - RMT (retic maturation time) = 1 for HCT 45%; 1.5 for HCT 35%; 2 for HCT 25%; 2.5 for HCT of 15%
Signs of RBC destruction

- High LDH
- High total (indirect) bilirubin
- Low haptoglobin
- Reticulocytosis
- Smear: fragmented RBCs, spherocytes

And, of course, appropriate H&P for hemolysis. Consider infection, sepsis, DIC, liver dz, Sickle cell, etc, etc.
Don’t forget about this guy

- History
- Exam
- Guaiac stool
- Targeted labs/imaging
Quick Quiz

The patient with the highest likelihood of having iron deficiency anemia is:

A. One year old male  
B. Adolescent black female  
C. Middle age black female  
D. 65 year old white female  
E. 75 year old white male
Quick Quiz

USPSTF recommends screening which of the following groups for iron deficiency anemia?

A. 6 month old infants
B. Menstruating adolescent females
C. Pregnant women
D. Women and men > 75 years old
E. All of the above
Quick Quiz

Which of the following impairs iron absorption?

A. Grapefruit juice
B. Orange juice
C. Red meat
D. Tea
E. Magneto
Case 1: “totally exhausted”

40 year old female presents with profound fatigue, slowly worsening over a period of weeks. PMH: unremarkable but is “medically homeless”. SH: nonsmoker, non-drinker, mother of 4, Jehovah’s Witness, homemaker.

CBC:
- WBC 0.8 k/ mm3
- RBC 1.72 m/ mm3
- Hgb 5.3 g/ dl
- HCT 18%
- Plts 99 k/ mm3
- MCV 114 fL
- MCH 31 pg
- MCHC 30%
- RDW 18.9%

Reticulocyte count: 54.3 K/mm3
What’s going on here?

Symptom of an underlying disease

Size/shape/characteristics

Production v. removal
Case 1

- More labs:
  - B12 level 46 pg/mL (that’s really low!)
  - Folate normal
  - Ferritin normal
- Diet was to blame
- Patient received B12 replacement subcutaneously
- CBC normalized
Case 2

19 year old female presents with several months of fatigue. She reports no other significant symptoms or PMH. Non-drinker, non-smoker, but drinks a lot of tea. Menses occurs at regular intervals but is heavy and lasts for 7 days.

PE: pale conjunctivae; otherwise normal.

Labs: Hgb 8.3 g/dL, MCV 79 fL, TSH normal.
Next step?

- Check ferritin
- Ferritin < 41 ng/mL is 98% sensitive and 98% specific for iron deficiency (note that UIHC reference range is 22-322).
- If ferritin < 15 ng/mL, likelihood ratio for iron deficiency is 41-51.
What if ferritin is normal?

May still be iron deficiency anemia since ferritin is an acute phase reactant.

Next steps:
- Check TIBC, serum iron, transferrin saturation

Still confused:
- Serum (or “soluble”) transferrin receptor – increased in iron deficiency, but not as sensitive or specific as ferritin

Further steps:
- Consider other diagnoses
- Hematology consult
- Bone marrow biopsy
- Therapeutic trial
How do you give a trial of iron therapy?

- Iron sulfate 300 mg = 60 mg of elemental iron (about $1/5^{th}$ is iron)
- Iron gluconate 325 mg = 36 mg of elemental iron (about $1/10^{th}$ is iron)
- Take with vitamin C or orange juice
- After 1 month, Hgb should rise by 1-2 g/dL; if not, reconsider diagnosis, confirm adherence and consider IV iron.
So, you diagnosed iron deficiency anemia and treated the patient. Looks like it’s Miller time! But wait…

Iron deficiency anemia is a symptom of an underlying disease.

Make the diagnosis.
IDA vs. ACD

Iron deficiency anemia
- History of blood loss without evidence of inflammatory disease
- Generally:
  - Ferritin – low
  - TIBC – high
  - Serum transferrin receptor – high

Anemia of chronic disease
- History of inflammatory disease without evidence of blood loss
- Elevation in other inflammatory markers (CRP, ESR)
- Generally:
  - Ferritin - normal or high
  - TIBC – low
  - Serum transferrin receptor – low

Typically, iron levels are low and MCV is low (or low normal) in both conditions.
Quick Quiz

Which patient is most likely to benefit from RBC transfusion?

A. A cute, happy baby with a hemoglobin of 10 mg/dl
B. 30 y.o. MVC victim with 1 L blood loss, no active bleeding, Hgb 10 g/dl after fluids
C. 40 y.o. female with sickle cell pain crisis and Hgb 7 g/dL
D. 75 y.o. male with acute MI and Hgb 10 g/dL
E. 80 y.o. healthy female with femur fracture requiring operative repair and Hgb 7 g/dL
Transfusion

What is the source of the universally agreed-upon guidelines for when to give a red cell transfusion?
AABB recommendations

- Hgb < 6 – transfuse unless exceptional circumstances
- Hbg 6-7 – transfusion generally indicated
- Hgb 7-8 – transfuse if postop, if known CV disease
- Hgb 8-10 – transfusion generally not indicated but consider if symptomatic, ongoing bleeding, ongoing ACS, etc
- Hgb > 10 – transfusion almost never needed
## 30-day mortality

<table>
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<tr>
<th>Source</th>
<th>Lower hemoglobin threshold</th>
<th>Higher hemoglobin threshold</th>
<th>Risk ratio (95% CI)</th>
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**Overall random effects model**

Heterogeneity: $I^2 = 0$ percent
Test for overall effect: $p = 0.10$
It’s midnight. You get a call that an anemic patient on 6RC is 30 minutes into his RBC transfusion. He is having dyspnea and back pain. Current HR 130, BP 88/50 (at 8 PM HR 100, BP 110/70). You ask the nurse to:

A. Stop the blood transfusion and begin normal saline through the IV.
B. Increase the rate of transfusion.
C. Administer acetaminophen 650 mg by mouth.
D. Administer furosemide 40 mg IV.
E. Place a nasogastric tube for lavage.
Quick Quiz

Mrs. Smith has a hemoglobin of 9 g/dL and an MCV of 90. She could not possibly have iron deficiency based on her normocytosis.

True or False and Why?
Questions?