ANEMIA: DIAGNOSIS AND MANAGEMENT

Ronald S. Go, MD
Chair, Classical Hematology
Mayo Clinic, Rochester, MN

97th Annual Clinical Reviews
November 7, 2023
DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

• Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

• Nothing to disclose
LEARNING OBJECTIVES

• Determine how to approach evaluation of anemia based on underlying pathophysiology
• Identify commonly performed tests that are of low value
• Discuss the treatment of nutritional anemias
OUTLINE

• 3 Cases
• Anemia evaluation in practice
• Treatment of iron and B12 deficiencies
• Pretest probability and rare diseases
• How I evaluate anemia
CASE #1: MICROCYTIC ANEMIA

A 43-year-old male was seen in the clinic for follow-up of type II diabetes mellitus. He reported bright red blood stain on his stools daily associated w/ hemorrhoids. He uses Asian folk medicines. Recent labs:

Which of the following is unnecessary?
1. Reticulocyte count
2. Blood smear
3. GI evaluation for blood loss
4. Hemoglobin electrophoresis
5. Lead level
CASE #1: RELEVANT QUESTIONS

• What are the common causes of anemia?
• When does bleeding cause anemia?
• What is the differential diagnosis of microcytic anemia?
ANEMIA

Blood Loss

- 60%
- 35%
- 5%

1. Big bleed
2. Small bleed, ONLY if iron deficient

Hemolysis

Decreased Production
# MICROCYTIC ANEMIAS

## Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>• Most common 70%</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>• CRP better than ESR</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>• Hgb-MCV delta &gt;2</td>
</tr>
<tr>
<td>Copper deficiency</td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td></td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td>• &lt;5%; don’t check unless risk factors or other signs present</td>
</tr>
<tr>
<td>Lead poisoning</td>
<td></td>
</tr>
</tbody>
</table>
IRON DEFICIENCY ANEMIA: DIAGNOSIS

**Ferritin**

- **≤30 µg/L**
  - Iron Deficient
  - No Inflammation

- **>30 µg/L**
  - **Inflammation**
    - **>200 µg/L**
      - Not Iron Deficient
    - **<200 µg/L**
      - sTfR-Ferritin Index
        - **<1**
          - Not Iron Deficient
        - **1-2**
          - Indeterminate
        - **>2**
          - Iron Deficient

**sTfR**, soluble transferrin receptor; **sTfR-ferritin index** = sTfR (mg/L) ÷ log [ferritin (mcg/L)]
IRON DEFICIENCY ANEMIA: TREATMENT

Method of Replacement

PO

Labs in 4 Weeks

Improved?

Yes

Reversible Cause

Stop After Normal Labs

No

Irreversible Cause

Indefinite Treatment

IV*

Labs in 2 Weeks

Ferritin >100?

Yes

Labs in 12 Weeks

Normal Labs

Reversible Cause

Stop Treatment

No

Irreversible Cause

Maintain Ferritin >100

Increase Dose or IV

Give Another Infusion

*Flat dose of ~1 gram per course of treatment.
## ORAL IRON REPLACEMENT STRATEGY: PHASE III TRIALS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Random</th>
<th>N</th>
<th>Population</th>
<th>Outcome</th>
<th>Results</th>
<th>P</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeSO₄ 60 mg PO¹</td>
<td>QOD x 28d</td>
<td>19</td>
<td>Hgb &gt;8, ferritin ≤25</td>
<td>Iron absorption/hepcidin</td>
<td>Lower/higher</td>
<td>&lt;0.05</td>
<td>Hgb 13.2 vs 12.8 at entry; Hgb 13.2 vs 13.6 (P=0.16)/ ferritin 23.6 vs 28.3 (P=0.058) at end</td>
</tr>
<tr>
<td></td>
<td>QD x 14d</td>
<td>21</td>
<td></td>
<td></td>
<td>Higher/lower</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FeSO₄ 120 mg PO¹</td>
<td>Single dose x 3d</td>
<td>20</td>
<td>Hgb &gt;8, ferritin ≤25</td>
<td>Iron absorption/hepcidin</td>
<td>Same/lower</td>
<td>&lt;0.05</td>
<td>Nausea and abdominal pain not significantly different between arms in both studies</td>
</tr>
<tr>
<td></td>
<td>Split dose x 3d</td>
<td></td>
<td></td>
<td></td>
<td>Same/higher</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FeSO₄ 100 mg PO 2 tabs²</td>
<td>QOD x 8wk</td>
<td>100</td>
<td>Hgb &lt;10, ferritin &lt;50</td>
<td>Mean ΔHgb at 8 wks</td>
<td>1.05 ± 1.34</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>FeSO₄ 100 mg PO 1 tab + Placebo PO 1 tab</td>
<td>QD x 8wk</td>
<td>100</td>
<td>CKD stage 3-4, TSAT ≤30%, ferritin ≤500</td>
<td>%TSAT at 12 wks</td>
<td>1.36 ± 1.51</td>
<td>0.27</td>
<td>Coefficient of -1.4; linear mixed effect model</td>
</tr>
<tr>
<td>Fe ascorbate 100 mg PO³</td>
<td>BID x 12wk</td>
<td>39</td>
<td>CKD stage 3-4, TSAT ≤30%, ferritin ≤500</td>
<td></td>
<td>Coefficient of -1.4; linear mixed effect model</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>QD x 12 wk</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CASE #1: MICROCYTIC ANEMIA

A 43-year-old male was seen in the clinic for follow-up of type II diabetes mellitus. He reported bright red blood stain on his stools daily associated with hemorrhoids. He uses Asian folk medicines. Recent labs:

Which of the following is unnecessary?
1. Reticulocyte count
2. Blood smear
3. GI evaluation for blood loss
4. Hemoglobin electrophoresis
5. Lead level

β Thalassemia minor
CASE #2: MACROCYTIC ANEMIA

60-year-old female presented with dyspnea on exertion and weight loss x 3 months. She has schizophrenia + depression and taking mirtazapine + risperidone for years. No alcohol use.

Labs:

Which of the following is unnecessary?

1. Vitamin B12
2. Folate
3. Reticulocyte count
4. Blood smear
5. TSH
CASE #2: RELEVANT QUESTIONS

• What is the differential diagnosis of macrocytic anemia?
• When should we check B12 or folate?
• How common is myelodysplastic neoplasm?
**MACROCYTIC ANEMIAS**

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>B12 deficiency</td>
</tr>
<tr>
<td>Folate deficiency</td>
</tr>
<tr>
<td>Reticulocytosis</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td>Cold agglutinin disease</td>
</tr>
<tr>
<td>Copper deficiency</td>
</tr>
</tbody>
</table>

**Macrocytosis w/o Anemia**

- ETOH use (unless abuse)
- Hypothyroidism
  - Generally, does not cause macrocytosis unless myxedema
- Liver disease
- Medications

<10%; don’t check unless risk factors or other signs present
LOW B12/FOLATE: NOT AS COMMON AS WE THINK

• B12 deficiency
  ✓ 2.7% of adult population¹
  ✓ Confirm with methylmalonic acid level
  ✓ Storage: 3-5 years
  ✓ Etiology not relevant in practice
  ✓ Rx: 1-2 mg PO QD; ²-³ IM initially if neurologic symptoms

• Folate deficiency
  ✓ <1% of adult population⁴
  ✓ Check only if risk factors present

MDS: ALSO, NOT AS COMMON AS WE THINK

• Annual incidence:\(^1\)
  ✔ 12,000 cases in US
  ✔ 3.6/100,000

• Hematologists/oncologist:\(^2\)
  ✔ US - 13,365 licensed
  ✔ Mayo Rochester – 60 hematologists/40 fellows

\(^1\)www.seer.cancer.gov.
\(^2\)JCO Oncol Pract 2022:18:396.
CASE #2: MACROCYTIC ANEMIA

60-year-old female presented with dyspnea on exertion and weight loss x 3 months. She has schizophrenia + depression and taking mirtazapine + risperidone for years. No alcohol use.

Labs:

Which of the following is unnecessary?

1. Vitamin B12
2. Folate
3. Reticulocyte count
4. Blood smear
5. TSH

Vitamin B12 deficiency
CASE #3: NORMOCYTIC ANEMIA

A 62-year-old female came to Mayo Clinic for evaluation of recurrent low-grade fevers and arthralgias x 3 months. CBC was normal 6 months ago.

Labs:

Which of the following is unnecessary?
1. Vitamin B12
2. Ferritin
3. Reticulocyte count
4. Blood smear
5. Serum protein electrophoresis
CASE #3: RELEVANT QUESTIONS

• What is the differential diagnosis of normocytic anemia?
• When does chronic kidney disease cause anemia?
• What to do/not to do before a hematology referral (for bone marrow biopsy)?
NORMOCYTIC ANEMIAS

**Differential Diagnosis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic inflammation</td>
<td>• Hgb &gt;9 g/dL</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>• eGFR &lt;30 mL/min</td>
</tr>
<tr>
<td>Hypogonadism (male)</td>
<td>• Hgb &gt;11.5 g/dL</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>• About half are normocytic</td>
</tr>
<tr>
<td>B12 deficiency</td>
<td>• Last in the list</td>
</tr>
<tr>
<td>Marrow pathology (malignant/</td>
<td>• Super rare</td>
</tr>
<tr>
<td>non-malignant)</td>
<td></td>
</tr>
</tbody>
</table>
MYELOMA: NOT AS COMMON AS WE THINK

• Annual incidence:¹
  ✓ 34,000 cases in US
  ✓ 7/100,000

• Hematologists/oncologists:²
  ✓ US - 13,365 licensed
  ✓ Mayo Rochester - 60 heme (12 myeloma MDs)

²JCO Oncol Pract 2022:18:396.
CASE #3: NORMOCYTGIC ANEMIA

A 62-year-old female came to Mayo Clinic for evaluation of recurrent low-grade fevers and arthralgias x 3 months. CBC was normal 6 months ago.

Labs:

Which of the following is unnecessary?
1. Vitamin B12
2. Ferritin
3. Reticulocyte count
4. Blood smear
5. Serum protein electrophoresis

Anemia of chronic inflammation
HOW I EVALUATE ANEMIA: A TIERED APPROACH
HOW I EVALUATE ANEMIA: A TIERED APPROACH
QUESTION #1
IS THE PATIENT BLEEDING?

Bleeding

- Clinical
  - Macroscopic
  - Microscopic
- Laboratory
  - Iron deficiency
- Yes
  - Evaluate
  - GI
- No
  - Production
  - Hemolysis
QUESTION #2
IS THIS A HYPOPROLIFERATIVE ANEMIA?

Production

- Clinical
  - No blood loss
- Laboratory
  - Low reticulocyte
- Yes
  - Evaluate
    - Marrow
- No
  - Hemolysis
TIERED TESTING

Basic
- Blood smear
- CBC
- Creatinine
- Ferritin
- Reticulocyte
- Vitamin B12

Advanced
- ALT/AST
- Bilirubin
- Copper
- CRP
- Folate
- Haptoglobin
- HemoQuant®
- LDH
- Marrow bx
- Testosterone

Specialty
- GI evaluation
- Rheum cons
- ADAMTS13
- Direct antiglobulin
- EMA
- Hgb electroph
- Mutation tests
- PNH flow
- Etc
QUESTIONS & DISCUSSION

go.ronald@mayo.edu