MICROCYTIC ANEMIA & NEW APPROACHES TO MANAGEMENT OF IRON DEFICIENCY

KELLY M. DAVIDSON, MD

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DISCLOSURES

American Board of Internal Medicine, Hematology Exam Committee
Takeda, research support
Sanofi Genzyme, advisory board

Discussion of off-label drug use: IV iron
OBJECTIVES

- Review the diagnosis of iron deficiency anemia
- Distinguish iron deficiency from other causes of microcytic anemia
- Discuss advances and controversies in iron repletion
  - Oral iron supplementation
  - Intravenous iron preparations
CASE 1

48-year old female with no PMH presents for follow-up after an urgent care visit over the weekend. Six months ago, she developed morning stiffness in both hands as well as bilateral foot and ankle pain. She has been more tired and has exertional dyspnea. She uses ibuprofen for the pain but takes no other medications.

She hands you a copy of labs obtained at the urgent care clinic:

- WBC 5.4 (normal 4-11 k/µL)
- Hemoglobin 9.7 (normal 12-16 g/dL)
- Hematocrit 28.7 (normal 35.0-47.0 %)
- Platelets 280 (normal 150-450 k/µL)
- MCV 78 fL (normal 83-95)
- Serum iron 19 (normal 40-145 µg/dL)
WHAT IS THE MOST LIKELY CAUSE OF HER ANEMIA?

- A. Iron deficiency
- B. Inflammation
- C. Hemoglobinopathy
- D. Need more information
THE GLOBAL BURDEN OF ANEMIA

Anemia burden is high, affecting 27% of the world’s population—1.93 billion people—in 2013.
Prevalence of Anemia by Etiology, 1990 and 2013
For both genders, iron deficiency is the most common cause of anemia globally.

Prevalence of Anemia by Etiology, 1990 and 2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td></td>
<td></td>
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<tr>
<td>2013</td>
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</table>

CLINICAL IMPLICATIONS OF IRON DEFICIENCY ANEMIA

- Increased symptom burden in IBD
  - Decreased QoL in IBD

- Decreased QoL in CKD
  - Increased pre-dialysis mortality and end-stage renal disease
  - Increased cardiovascular hospitalizations in CKD

- Paleness
  - Alopecia, dry and damaged hair
  - Dry and rough skin
  - Nail abnormalities and koilonychia
  - Oral lesions and atrophic glossitis

- Increased morbidity, mortality, hospital length of stay, and re-admissions in major surgery

- Headache, vertigo, syncope
  - Cognitive impairment in children and elderly
  - Restless leg syndrome

- Fatigue, tachycardia, cardiac murmur, angina, dyspnoea
  - Poor physical performance and QoL in all age groups
  - Increased hospitalizations, decreased exercise tolerance, QoL, and survival in CHF

- Increased hospitalization and decreased QoL in heavy menstrual bleeding
  - Increased risk of preterm labour, low neonatal weight, perinatal complications, newborn and maternal mortality in pregnancy

- Haemodynamic instability
  - Decreased immune response

IRON BALANCE

- Normal body iron content 3-4 grams
- Daily requirement 25mg, with 20mg needed to produce 200 billion red blood cells daily
- Iron lost in sweat, shed skin cells, +/- GI loss- 1mg/day
- Premenopausal women lose an extra 0.5-1.0mg/day due to menses
- Losses usually balanced by intake- absorption of 10% of the 10-20mg of daily iron in typical Western diet
- Losses are unregulated, thus iron homeostasis mainly controlled by regulating iron supply

A. Normal

B. Absolute iron deficiency

C. Functional iron deficiency

Inflammation
The Microcytic Anemias (MCV < 80 fL)

Iron deficiency
Anemia of inflammation

Iron

Protoporphyrin

Sideroblastic anemia

Globin

Thalassemia

Heme

Hemoglobin

# Labs to Distinguish Causes of Microcytic Anemia

<table>
<thead>
<tr>
<th>Test</th>
<th>Iron deficiency Anemia</th>
<th>Anemia of inflammation</th>
<th>Thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin</td>
<td>↓</td>
<td>Normal to ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Serum iron</td>
<td>↓</td>
<td>↓</td>
<td>Normal to ↑</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>↓</td>
<td>↓</td>
<td>Normal to ↑</td>
</tr>
<tr>
<td>Total iron-binding capacity</td>
<td>↑</td>
<td>Normal to ↓</td>
<td>Normal</td>
</tr>
<tr>
<td>RDW</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
DETERMINATION OF IRON STATUS

- Serum ferritin - most reliable initial test
- Ferritin ≤ 30 µg/L (sensitivity 92%, specificity 98%)
- Acute-phase reactant, increases with age, so consider the entire picture
- Good rule of thumb: ferritin < 100 µg/L in the setting of inflammation may indicate iron deficiency (with transferrin saturation < 20%)
- Other tests:
  - Serum soluble transferrin receptor ↑
  - Reticulocyte Hb concentration ↓
  - Hepcidin level ↓
  - Bone marrow iron stores ↓

DIFFERENTIAL DIAGNOSIS OF A LOW SERUM FERRITIN

- Iron deficiency
- Iron deficiency
- Iron deficiency
INVESTIGATE THE CAUSE

**Decreased Iron Availability**

<table>
<thead>
<tr>
<th>Intake/Absorption</th>
<th>Sequestration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary restriction</td>
<td>Inflammatory diseases</td>
</tr>
<tr>
<td>Antacid/PPI medication</td>
<td>CHF</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>CKD</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>Obesity</td>
</tr>
<tr>
<td>Gut resection</td>
<td>IRIDA</td>
</tr>
<tr>
<td>GERD/Gastritis</td>
<td></td>
</tr>
<tr>
<td><em>H. Pylori</em> infection</td>
<td></td>
</tr>
<tr>
<td>High caffeine, tea, calcium</td>
<td></td>
</tr>
</tbody>
</table>

**Physiologic State**

- Pregnancy
- Childhood
- Extreme exercise

**Blood Loss**

- Vaginal
- Gastrointestinal
- Genitourinary
- Iatrogenic
- Blood donation
- Epistaxis

**Increased Iron Need**

PPI: Proton pump inhibitor; GERD: gastro-esophageal reflux disease; CHF: congestive heart failure; CKD: chronic kidney disease; IRIDA: iron refractory iron deficiency anemia (rare form of genetic iron deficiency)
CASE 2

A 25-year old woman presents for an annual exam. She endorses menorrhagia and fatigue. She notes a peculiar craving to chew on crushed ice. She denies chest pain or shortness of breath at rest, but is tired when taking the stairs. She has no prior PMH and takes no medications.

Exam: Temp 36.5, HR 85, BP 115/72, RR 16, O2 sat 98%
She appears fatigued and has conjunctival pallor. Normal heart, lung and abdominal exams.

Labs:
Hb 9.2 (normal 12-16 g/dL)
Hct 27.4 (normal 35.0-47.0 %)
MCV 73.0 (normal 83.0-95.0)
MCH 21.2 (normal 28.0-32.0)
Ferritin 3 (normal 20 - 275 ng/mL)
Serum Iron 20 (normal 60-160 ug/dL)
Iron saturation 4 % (normal, 16-48 %)
Transferrin 354 (normal, 190 - 315 mg/dL)
IN ADDITION TO MANAGING HER MENORRHAGIA, WHICH OF THE FOLLOWING SHOULD YOU RECOMMEND NOW?

A. Ferrous sulfate 325mg po TID with vitamin C  
B. IV iron infusion  
C. Ferrous sulfate 325mg po QOD with vitamin C  
D. Blood transfusion
Don't transfuse RBCs for iron deficiency without hemodynamic instability

Preoperative patients with iron deficiency and patients with chronic iron deficiency without hemodynamic instability (even with low Hb levels) should be given oral and/or intravenous (IV) iron
TREATMENT OF Iron DEFICIENCY

- Cause of iron deficiency should be addressed in all cases and eliminated when possible
- Choice of iron compound and route of administration depends upon:
  - Degree of anemia
  - Reversibility of the underlying cause
  - Clinical status (age, sex, longstanding vs recent onset)
  - Cost, availability
  - Patient preference
ORAL IRON SUPPLEMENTATION

- Iron salts (ferrous sulfate, fumarate, gluconate) are standard first-line
  - Inexpensive, readily available, often effective
  - Other preparations - heme iron polypeptide and polysaccharide iron complexes

- Traditionally, 100-200 mg elemental iron per day was recommended
  - Ferrous sulfate (generally 20 to 30% elemental iron per mg of mineral salt) po TID

- Adverse effects common (N/V, constipation, diarrhea, metallic taste, dark stool)
  - Only about 10-15% of elemental iron ingested is absorbed
  - Unabsorbed iron contributes to side effects
  - Non-compliance in 30-70% of cases

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HOW SHOULD WE DOSE ORAL IRON?

- Inflammation
- High plasma iron levels
- High iron stores

**HEPCIDIN**

- Iron deficiency
- Erythropoiesis
- Hypoxia

Iron absorption blocked
ORAL IRON AND THE HEPCIDIN EFFECT

- 54 nonanemic but iron-depleted young women (ferritin ≤20 µg/L) using 3 isotopes of iron
- Quantified the magnitude and duration of the acute iron-induced increase in hepcidin at different FeSO4 doses
- Measured total and fractional iron absorption in several scenarios testing varying doses of oral iron administered over a variety of schedules

Ingesting a substantial single dose of oral iron led to an increase in plasma iron, which in turn led to an increase in hepcidin. This increase in hepcidin then impaired iron absorption from subsequent doses of iron. The hepcidin effect in suppressing iron absorption could last as long as 48 hours. Iron absorption was best when dosing was restricted to lower doses and less frequent administration (40 to 80 mg of iron no more than once a day). Two small open-label trials subsequently confirmed these findings; clinical trials ongoing.

Should we be giving a single substantial dose of elemental ferrous iron on Monday, Wednesday, and Friday?
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Example</th>
<th>Dose per tablet (mg)</th>
<th>Elemental iron content per tablet (mg)</th>
<th>Dose</th>
<th>Special instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron salts</td>
<td>Ferrous gluconate</td>
<td>240</td>
<td>27</td>
<td>1-3 tablets, once per day or once every other day</td>
<td>Take on empty stomach; consider vitamin C; take at a different time of day than antacid or proton pump inhibitor. Acidic environment required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>325</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ferrous sulfate</td>
<td>325</td>
<td>65</td>
<td>1-2 tablets, once per day or once every other day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ferrous fumarate</td>
<td>325</td>
<td>106</td>
<td>1 tablet, once per day or once every other day</td>
<td></td>
</tr>
<tr>
<td>Heme iron polypeptide</td>
<td>Proferrin</td>
<td>398</td>
<td>11</td>
<td>1-3 tablets per day</td>
<td>Can be taken with a meal. Acidic environment not required for absorption.</td>
</tr>
<tr>
<td>Polysaccharide iron complex</td>
<td>Feramax</td>
<td>150</td>
<td>150</td>
<td>1 tablet once per day</td>
<td>Can be taken with a meal. Acidic environment not required for absorption.</td>
</tr>
</tbody>
</table>
RESPONSE TO ORAL IRON

- Peak retic count: 7-10 days
- Increased Hb/Hct: 14-21 days
- Normal Hb/Hct: 6-8 weeks
- Normal iron stores: 3-6 months
PEARLS AND PITFALLS WITH ORAL IRON SALTS

- Take on empty stomach
- Add vitamin C/OJ to augment absorption
- Calcium-containing foods/beverages, phytates (cereal grains), tannins (tea), antacids will inhibit absorption
- Repeat iron studies when fasting/holding morning dose of iron
- Avoid enteric-coated/sustained-release preparations
- FOBT results not affected
- Usually treat until iron stores replaced (aim for ferritin 50-100)
ORAL IRON FAILURE?

- Incorrect diagnosis (eg thalassemia, anemia of inflammation)
- Other concurrent issues (eg B12, folate deficiencies)
- Patient is not taking it
- Patient is not absorbing it
- Rapid blood loss exceeds iron intake
- Therapy worked but bleeding recurred
A 56 year-old male presents to clinic for evaluation. He reports generalized weakness, exertional dyspnea and insomnia due to restless legs.

PMH of GERD, HTN and obesity. He underwent gastric bypass surgery 8 years ago.

He takes lisinopril and famotidine daily.

Labs demonstrate a microcytic, hypochromic anemia with iron deficiency

- Hb 8.8 g/dL  
- MCV 73.0 fL  
- Ferritin 6 ng/mL
WHAT SHOULD YOU RECOMMEND NOW?

A  Ferrous sulfate 325mg po every other day
B  Blood transfusion
C  IV iron
D  Ferrous sulfate 325mg po TID
## INDICATIONS FOR IV IRON

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral iron intolerance</td>
<td>Persistent GI adverse effects</td>
</tr>
<tr>
<td>Oral iron refractoriness</td>
<td>Defective absorption: gastrectomy, duodenal bypass, bariatric surgery</td>
</tr>
<tr>
<td></td>
<td>Intestinal disorders: eg IBD, atrophic gastritis, <em>H pylori</em> infection, celiac disease</td>
</tr>
<tr>
<td></td>
<td>Genetic forms (IRIDA)</td>
</tr>
<tr>
<td></td>
<td>No Hb improvement after 4 weeks of oral therapy</td>
</tr>
<tr>
<td>Severe anemia (Hb &lt; 7-8 g/dL)</td>
<td>Need for rapid Hb improvement</td>
</tr>
<tr>
<td>2nd and 3rd trimesters of pregnancy</td>
<td>Need for rapid Hb increase; often intolerance to oral iron</td>
</tr>
<tr>
<td>ESA treatment</td>
<td>More effective than oral iron in CKD; cancer</td>
</tr>
<tr>
<td>Chronic blood loss difficult to manage with oral iron</td>
<td>Heavy uterine bleeding, chronic GI bleeding, hereditary disorders of hemostasis, HHT</td>
</tr>
<tr>
<td>Other</td>
<td>Perioperative for major surgery with significant estimated blood loss and demonstrated iron deficiency</td>
</tr>
<tr>
<td></td>
<td>Chronic systolic heart failure</td>
</tr>
</tbody>
</table>

USE OF IV IRON PREPARATIONS

- High molecular weight iron dextran no longer used
- Formulas exist to calculate required dose (body weight, current Hb, amount of iron in product)
- Total body iron stores in adults are generally in the range of 5 mg/kg in women, 10 mg/kg in men.
- Correction of anemia plus repletion of iron stores may require up to a gram or more of elemental iron.
- Common approach- treat with 1000 mg initially and reassess at 4 weeks
<table>
<thead>
<tr>
<th>Compound</th>
<th>Brand name</th>
<th>Recommended amount per dose</th>
<th>Infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMW Iron Dextran</td>
<td>INFeD</td>
<td>1000 mg after 25-mg test dose</td>
<td>2-6 hr (+ test dose)</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>Ferrlecit</td>
<td>125 mg</td>
<td>12.5 mg/min</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>Venofer</td>
<td>200-300 mg</td>
<td>100 mg/30 min</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>Feraheme</td>
<td>510 mg</td>
<td>15 min</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>Injectafer</td>
<td>750 mg</td>
<td>15 min</td>
</tr>
<tr>
<td>Iron isomaltoside</td>
<td>Monofer</td>
<td>≤1000 mg</td>
<td>&gt;15 min</td>
</tr>
</tbody>
</table>
ADVERSE EVENTS WITH NEWER IV IRON FORMULATIONS

- Minor/moderate infusion reactions (1:200)
  - Chest/back pain
  - Headaches
  - Nausea
  - Arthralgia, myalgia
  - Flushing
  - Pruritus

- Severe hypersensitivity (<1:200,000)
  - Hives
  - Stridor
  - Wheezing
  - Hypotension
  - Periorbital edema
  - Dyspnea

- Avoid with active infection

- Hypophosphatemia (FCM)
PEARLS/PITFALLS WITH IV IRON

- Administer IV iron product slowly and observe for infusion reaction
- Don’t routinely pre-medicate (unless asthma or multiple drug allergies)
- Similar rates of reactions among these products
- Choice of product depends on cost, number of visits, time to administer
- Generally wait 4 weeks to repeat iron studies
- May affect MRI results up to 3 months (ferumoxytol)
PATIENT BLOOD MANAGEMENT/IV IRON INITIATIVES AT UVA

- Pregnancy
- Pre-operative anemia
- Chronic gynecologic bleeding
TAKE HOME POINTS

- **Identify** iron deficiency and distinguish it from other causes of microcytic anemia
- **Investigate** the cause
- **Replace iron**: Oral vs IV?
  - Consider every other day dosing of oral iron salts
  - IV iron appropriate in a growing number of patients
QUESTIONS/COMMENTS

- Kelly Davidson
  - km6ft@virginia.edu
- UVA Hematology Referrals: 434-924-9333
- THANKS!