Iron deficiency anemia

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Disclosures

• Research funding: Agios Pharmaceuticals, Inc.

✓ This talk will mention iron isomaltoside, not currently available in the USA.
✓ It will not address iron deficiency anemia in pediatric patients.
Objectives

By the end of this lecture, you should be able to:

• Understand the pathophysiology of iron deficiency anemia in light of 21st century knowledge of iron metabolism;

• Diagnose iron deficiency by interpreting appropriate laboratory tests;

• Prescribe oral or parenteral iron treatment according to the latest evidence.
Why talk about iron deficiency anemia?

Global Burden of Disease, 2017

- Yemen – 50.01%
- India – 28.31%
- USA – 4.41%

India – 383 million
- Yemen – 14.9 million
- USA – 13.4 million
Where does iron come from?
Iron in the human body is exogenous
Physiology of iron metabolism

- **Dietary iron**
- **DUODENUM**
  - Absorption 1-2mg/day
- **LIVER**
  - 1000mg Fe
- **MACROPHAGES**
  - 600mg Fe
- **BONE MARROW**
  - 300mg Fe
- **ERYTHROCYTES**
  - 1800mg Fe

**HOW DO WE LOSE IRON?**

- **LOSSES**
  - 1-2mg Fe
Iron loss

Physiology:
- Menstrual bleeding
- Intestinal epithelial turnover

Excessive loss:
- Menorrhagia
- GI tract
- Nasal mucosa
- Hematuria/hemoglobinuria
- Frequent blood donation
- Etc…
Non-heme iron absorption

Transferrin

HEPHAESTIN

FERROPORTIN

Enterocyte

DMT1

FERROPORTIN

DCYTB

HEPHAESTIN

Fe$^{3+}$

Fe$^{2+}$

Fe$^{3+}$

Fe$^{2+}$
Ferroportin is the receptor for hepcidin

Nemeth et al., Science, 2004
High hepcidin causes intracellular iron retention, therefore it also **blocks absorption**.
Hepcidin: iron traffic control
Iron-poor diet

DUODENUM

Absorption

LIVER

Plasma transferrin

RBCs

BONE MARROW

MACROPHAGES

Absolute iron deficiency causes LOW hepcidin and HIGH ferroportin to increase absorption.
Erythropoiesis

• 3 main events:
  1. Decrease in size
  2. Change in color (hemoglobinization)
  3. Ejection of the nucleus

Source: www.as.miami.edu
Stages of erythropoiesis

MULTIPLICATION
- Proerythro
  - basophilic
  - polychromatophilic
  - orthochromatophilic
- reticulocyte
- mature erythrocyte

DIFFERENTIATION
- Stem cell
- BFU-E
- CFU-E
  - SCF, IL-3, EPO
  - Medullary stroma

HEMOGLOBINIZATION
- Iron
Anemias of the hemoglobinization stage (microcytic, MCV<80fL)

• Components of hemoglobin
  • Iron
  • Globin
  • Heme
Anemias of the hemoglobinization stage

- **Iron** deficiency
  - Absolute: iron deficiency anemia
  - Functional: anemia of inflammation /chronic disease

- **Globin** deficiency
  - Thalassemias

- **Heme** deficiency
  - Hereditary sideroblastic anemia
    - ALA synthase mutation (*ALAS2* gene)
  - Chronic lead poisoning
    - ALA synthase inhibition
How do we evaluate iron deficiency?
Diagnosis of iron deficiency anemia

• **Complete blood count**

  1. **Low red blood cell production:** low Hb, Hct, and RBCs
     • Thalassemia traits have compensatory normal or borderline RBC counts
  2. **Low marrow response:** reticulocytes are normal or low
     • High reticulocytes (>100k) – think acute bleeding or hemolysis!

• **Biochemical evidence of iron depletion**
## “Iron studies”

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference range (UWMC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (ng/mL)</td>
<td>10-180 (female)</td>
</tr>
<tr>
<td></td>
<td>20-230 (male)</td>
</tr>
<tr>
<td>Serum iron (mcg/dL)</td>
<td>31-171</td>
</tr>
<tr>
<td>Total iron binding capacity (mcg/dL)</td>
<td>270-535 (female)</td>
</tr>
<tr>
<td></td>
<td>250-460 (male)</td>
</tr>
<tr>
<td>Serum transferrin (mg/dL)</td>
<td>192-382 (female)</td>
</tr>
<tr>
<td></td>
<td>180-329 (male)</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>10-45 (female)</td>
</tr>
<tr>
<td></td>
<td>15-50 (male)</td>
</tr>
</tbody>
</table>

**CAUTION**: patients tested after taking supplements may have discrepancies
Iron-responsive elements and proteins: the IRE-IRP system

High iron

Low iron

5' ferritin

5' transferrin

3' ferritin

3' transferrin
Normal ferritin
Normal serum iron
Normal TIBC
Normal TSAT

Plasma

liver
Low ferritin
Low serum iron
High TIBC
Very low TSAT (<5%)
Diagnosis of iron deficiency anemia

• **Complete blood count**
  1. **Low red blood cell production**: low Hb, Hct, and RBCs
  2. **Low marrow response**: reticulocytes are normal or low
     • High reticulocytes (>100k) – think acute bleeding or hemolysis!

• **Biochemical evidence of iron depletion**
  1. Low ferritin
  2. Low transferrin saturation (<20%, but typically <10%)
  3. High TIBC

• Iron deficiency without anemia exists and needs treatment!
  • Isolated low ferritin, TSAT trending down
Causes of iron deficiency

• Always investigate bleeding (GI, Gyn, epistaxis, hematuria...)
• Malabsorption
  • Surgical (gastric bypass)
  • Inflammatory bowel diseases
  • Parasites (hookworm)
  • Atrophic gastritis
  • Prolonged use of medications (e.g. PPI)
• Vegetarian or vegan diet DOES NOT justify iron deficiency by itself (but beware of the weird/radical diets)
Treatment and monitoring of iron deficiency anemia

• Goals:
  • Hb>12 women, Hb>13 men
  • Normal MCV (>80fL) and MCH (>28pg)
  • Ferritin >20 for women, >30 for men
  • Transferrin saturation above 20%

• Treat or control cause!
• Return with labs in 2 weeks can be helpful;
  • treatment adherence / side effects
  • reticulocyte count and hemoglobin equivalent

• Check CBC at least monthly until goals are reached.
Oral iron formulations

- Ferrous sulfate
- Ferrous fumarate
- Ferrous gluconate
- Ferric maltol
- Polysaccharide iron
- Carbonyl iron
- Ferric citrate
- Ferrous ascorbate
- Ferrous succinate
- Sucrosomial iron
Common questions about PO iron

• “On an empty stomach”? 

• “With orange/citric juice”? 

• “Add Vitamin C”? 

• “How many pills?” 

• “Once or twice daily?”
Oral iron for iron-depleted women: consecutive vs. alternate days
Oral iron for iron-depleted women: once vs. twice daily
Oral iron for iron deficiency anemia
Parenteral iron

• Intramuscular – NEVER!

• Intravenous – common misconceptions
  • “high risk of reaction” – HMW dextran
  • “last resort”
  • “needs faster recovery”

Intravenous iron formulations

- Low molecular weight dextran
- Iron gluconate
- Iron sucrose
- Iron polymaltose
- Iron isomaltoside
- Ferumoxytol
- Ferric carboxymaltose
### Table 4. Iron Preparations for Intravenous Use.*

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dose per Infusion</th>
<th>Maximum per Single Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric gluconate (Ferlecit)</td>
<td>125 mg/10–60 min</td>
<td>250 mg/60 min</td>
</tr>
<tr>
<td>Iron sucrose (Venofer)</td>
<td>100–400 mg/2–90 min</td>
<td>300 mg/2 hr</td>
</tr>
<tr>
<td>Low-molecular-weight iron dextran (INFeD)†</td>
<td>100 mg/2 min</td>
<td>1000 mg/1–4 hr</td>
</tr>
<tr>
<td>Ferumoxytol (Feraheme)†</td>
<td>510 mg/&gt;1 min</td>
<td>510–1020 mg/15–60 min</td>
</tr>
<tr>
<td>Ferric carboxymaltose (Ferinject)†</td>
<td>750–1000 mg/15–30 min</td>
<td>750–1000 mg/15–30 min</td>
</tr>
<tr>
<td>Iron isomaltoside (Monofer)‡‡</td>
<td>20 mg/kg of body weight/15 min</td>
<td>20 mg/kg of body weight/15 min</td>
</tr>
</tbody>
</table>

* Data are adapted from Powers and Buchanan13 and Auerbach and Ballard66
† Drugs that can be administered as a total dose in a single infusion.
‡‡ Iron isomaltoside is licensed for use only in Europe.
Oral or IV?

• An example using IBD

Table 2 | Rank probability matrix, as calculated by the Markov chain Monte Carlo method (see methods section), displaying estimated ranks of the different treatment effects. For each treatment, the table shows the probability that treatment effect was the best, 2nd best, 3rd best or 4th best of the four treatments compared.

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Best</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric carboxymaltose</td>
<td>0.82895</td>
<td>0.15245</td>
<td>0.01750</td>
<td>0.00110</td>
</tr>
<tr>
<td>Iron isomaltose</td>
<td>0.14675</td>
<td>0.32780</td>
<td>0.39715</td>
<td>0.13430</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>0.02365</td>
<td>0.49900</td>
<td>0.34385</td>
<td>0.13350</td>
</tr>
<tr>
<td>Oral iron</td>
<td>0.00065</td>
<td>0.02675</td>
<td>0.24150</td>
<td>0.73110</td>
</tr>
</tbody>
</table>
Oral vs. IV - IronWoMan trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oral</th>
<th>IV</th>
<th>p between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (venous), g/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V0</td>
<td>11.7 (11.3–12.4)</td>
<td>11.6 (11.0–12.1)</td>
<td>.106</td>
</tr>
<tr>
<td>V1</td>
<td>13.6 (13.0–14.2)</td>
<td>13.6 (13.0–14.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transferrin Sat, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V0</td>
<td>9.0 (6.0–14.0)</td>
<td>7.5 (6.0–12.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V1</td>
<td>21.0 (16.0–32.0)</td>
<td>27.0 (23.0–35.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V0</td>
<td>7 (5–10)</td>
<td>5 (4–9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V1</td>
<td>25 (17–34)</td>
<td>105 (75–145)</td>
<td></td>
</tr>
<tr>
<td>Phosphate, mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V0</td>
<td>0.97 (0.87–1.07)</td>
<td>0.99 (0.89–1.08)</td>
<td>0.860</td>
</tr>
<tr>
<td>V1</td>
<td>0.96 (0.83–1.10)</td>
<td>0.96 (0.86–1.10)</td>
<td></td>
</tr>
<tr>
<td>p in the groups</td>
<td>0.969</td>
<td>0.729</td>
<td></td>
</tr>
</tbody>
</table>

Side effects reported by participants by group.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>IV group</th>
<th>Oral group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstipation</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Tiredness</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Meteorism</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>General indisposition</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Fever</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal fullness</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Sensation of heat</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Pain in joints and muscles</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Gripe/colics</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Skin rash/itching</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hematoma at injection site</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Hyperpigmentation after IV iron

Thompson et al., Int Med J 2014

Gan & Orringer, Dermatol Surg 2015
Hypophosphatemia and hypersensitivity

• Known complication of several intravenous iron formulations
• Hypophosphatemia was more frequent in FCM (50%) than with ISM (5%)
• Hypersensitivity reactions were 4 times more frequent in ISM than in FCM

Bager et al., Br J Clin Pharmacol 2017, 83:118-1125
Detlie et al., Aliment Pharmacol Ther 2019, 50:397-406
When to consider IV iron?

- Intolerance to oral iron
- Failure to oral iron
- Ongoing blood loss that exceeds oral iron absorption
- Anatomic condition, malabsorption
  - Gastric bypass
  - Inflammatory bowel disease
- Peri-operative?
- Inflammation?
- Patient preference
MACROPHAGES

Dietary iron

DUODENUM Absorption

LIVER

Absorption

Plasma transferrin

RBCs LOSSES

BONE MARROW

Hepcidin

ANEMIA OF INFLAMMATION

Inflammation (IL-6)

Infection (LPS)

MACROPHAGES

LOSSES
Normal/high ferritin
Low serum iron
Low TIBC
Low TSAT (5-15%)
Anemia of inflammation vs. Iron deficiency

• **TIBC** is the clue to intracellular iron!
• Complex cases:
  • Liver disease (low Tf production)
  • Nephrotic syndrome (Tf loss)
  • Inflammation associated with iron deficiency
• Consider:
  • Serum transferrin
  • Soluble transferrin receptor (elevated in IDA)
    • sTfR/log ferritin index
  • Bone marrow iron? (still the gold standard)
  • Empirical iron therapy? (most used strategy – think IV)
  • Serum hepcidin (future?)
Iron deficiency in heart failure

148 anaemic patients with CHF

- False anaemia
  - 5 patients
- Normocytic anaemia
  - 105 patients
    - Renal failure
      - 35 patients
      - Iron deficiency
        - 6 patients
- Macrocytic anaemia
  - 7 patients
- Microcytic anaemia
  - 31 patients
    - Folate deficiency
      - 7 patients
    - Iron depleted status
      - 2 patients
    - β-thalassaemia
      - 8 patients

64 patients 21 patients
Chronic disease anaemia

Figure 1. Causes of anaemia in our population of CHF patients.

Opasich et al. Eur Heart J 2005;26:2232-2237
Defining iron deficiency in heart failure: serum markers vs. bone marrow iron

Grote Beverborg et al, *Circ Heart Fail.* 2018;11:e004519
TSAT and serum iron in HF

Grote Beverborg et al, Circ Heart Fail. 2018;11:e004519
Take home messages

• Iron deficiency is common, but often inadequately treated.
• Always look for the cause and treat it!
• Don’t stop treatment before iron stores are replenished.
• PO iron is probably best given once daily on alternate days to maximize absorption and decrease side effect
• Always offer PO iron and discuss pros and cons of IV iron with patient.
Questions?

towards better care for iron disorders

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