Update on iron deficiency
and supplementation

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Faculty Disclosures

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  - Other: none

Objectives

- Review the absorption of iron
- Distinguish between IDA and ACD
- Review the strategies for iron supplementation
  - Oral, IM, IV, blood transfusion
Iron Deficiency Syndromes

Auerbach et al. Best Practice & Research Clinical Gastroenterology 2013; 27: 131–140

Principles of iron absorption

Risvi. Am J Gastroenterol 2011; 106: 1872–1879

Iron Deficiency Symptoms

- Anemia
  - Reduced performance, fatigue
  - Headache
  - Dizziness
  - Tachycardia, dyspnea
- Non-hematological
  - Hair loss
  - Paresthesia of hand and feet
  - Restless leg syndrome

Stein & Dignass. Ann Gastro 2013; 26: 104 - 113
**Laboratory Findings in Anemia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anemia of Chronic Disease</th>
<th>Iron Deficiency Anemia</th>
<th>Both Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Reduced to normal</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Reduced</td>
<td>Reduced to increased</td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>Reduced to increased</td>
<td>Reduced</td>
<td>Reduced to normal</td>
</tr>
<tr>
<td>Solute transferrin receptor</td>
<td>Normal</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Ratio of solute transferrin receptor to log ferritin</td>
<td>Low (&lt;1)</td>
<td>High (&gt;2)</td>
<td>High (&gt;2)</td>
</tr>
<tr>
<td>Cytokine levels</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**Approach to Iron Deficiency Workup**

**Anemia of Chronic Disease**

Associated Diseases: General: 18.7%**2**

<table>
<thead>
<tr>
<th>Associated Disease</th>
<th>Estimated Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections (acute and chronic)</td>
<td>18.7%<strong>2</strong></td>
</tr>
<tr>
<td>Parasites</td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>22.9%<strong>1</strong></td>
</tr>
<tr>
<td>Sideroblastic</td>
<td>8.2%<strong>3</strong></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>8.2%<strong>3</strong></td>
</tr>
</tbody>
</table>

**References:**

### Oral Iron Absorption


### Bivalent versus trivalent iron

Santiago. Scientific World J. Volume 2012; Article ID 846824

### Comparison of Oral Iron Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Brand Name</th>
<th>% Elemental Iron (% w/w)</th>
<th>Dosage Form</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumarate</td>
<td>Palafir</td>
<td>33</td>
<td>Tablets; chewable tabs</td>
<td></td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>Floradix</td>
<td>22</td>
<td>Tablets</td>
<td></td>
</tr>
<tr>
<td>Ferric sulfate</td>
<td>Fer-In-Sol; Feridan</td>
<td>30</td>
<td>Oral elixir; Tablets; Enteric coated tablets</td>
<td></td>
</tr>
<tr>
<td>Heme iron polypeptide</td>
<td>Proferin</td>
<td>100</td>
<td>Capsules</td>
<td>High extracted from bovine RBC</td>
</tr>
<tr>
<td>Polysaccharide iron complex</td>
<td>Triferexx</td>
<td>100</td>
<td>Capsules; solution</td>
<td>Ferric iron complexed to hydrolyzed starch</td>
</tr>
</tbody>
</table>
Iron Replacement Dose Estimates

<table>
<thead>
<tr>
<th>Hemoglobin (g/dL)</th>
<th>Iron Replacement (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 12</td>
<td>1000</td>
</tr>
<tr>
<td>9 - 12</td>
<td>750</td>
</tr>
<tr>
<td>&lt; 9</td>
<td>500</td>
</tr>
</tbody>
</table>

A. Calculated total oral dose of elemental iron for acute correction. Additional doses of iron may be required to replace iron stores.


Tolerability of Oral Iron

Relative Cost of Iron Formulations

<table>
<thead>
<tr>
<th>Iron preparation</th>
<th>Brand name</th>
<th>Recommended dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>Serafin, Fer-Gan-Sol, Fer-In-Sol</td>
<td>325 mg (50 mg elemental) 3 times/day</td>
<td>$2.90/100 g tablet</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>Target</td>
<td>350 mg (50 mg elemental) 3 times/day</td>
<td>$6.02/100 g tablet</td>
</tr>
<tr>
<td>Ferric fumarate</td>
<td>Ferrion, Ferrada, Ferra-Quam, Tectin</td>
<td>314 mg (50 mg elemental) 3 times/day</td>
<td>$8.38/100 g tablet</td>
</tr>
<tr>
<td>Oral iron</td>
<td>Calcium carbonate, iron (325 mg elemental)</td>
<td>80 mg (25 mg elemental) 3 times/day</td>
<td>$0.31/100 g tablet</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>Dextrin (50 mg elemental)</td>
<td>80 mg (25 mg elemental) 3 times/day</td>
<td>$0.31/100 g tablet</td>
</tr>
<tr>
<td>Ferric succinate</td>
<td>Target</td>
<td>125 mg (50 mg elemental) 3 times/day</td>
<td>$1.05/30 mg dose</td>
</tr>
<tr>
<td>Ferric phos.</td>
<td>Target</td>
<td>125 mg (50 mg elemental) 3 times/day</td>
<td>$1.05/30 mg dose</td>
</tr>
<tr>
<td>Ferric phos.</td>
<td>Target</td>
<td>125 mg (50 mg elemental) 3 times/day</td>
<td>$1.05/30 mg dose</td>
</tr>
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Am J Gastroenterol 2011;106:1872-1879
Intramuscular Iron

- Painful
- Associated with gluteal sarcomas
- Permanent discoloration of skin
- Use not advocated

Auerbach et al. Am J. Hematol 2008; 83: 580 - 588

Indications for Parenteral Iron

- High iron requirements:
  - gastrointestinal bleeding
  - Menorrhagia
  - chronic haemodialysis
- Iron malabsorption
  - gastric resection, plication, or bypass
  - atrophic gastritis
  - coeliac disease
- Failure of oral therapy
  - gastrointestinal side-effects
  - poor adherence


Indications for IV Iron – Miami Experience

Wansch et al. 2013
Intravenous Iron Metabolism

- Iron-CHO complexes mix with plasma and phagocytosed by the reticuloendothelial system
- Within phagocytes, iron is released
  - Incorporated by ferritin into intracellular stores
  - Released to transferrin (extracellular iron binding protein)
  - Then delivered to transferrin receptors on surface of erythroid precursors and internalized for hemoglobin synthesis


Intravenous iron preparations

<table>
<thead>
<tr>
<th>Iron Preparation</th>
<th>Iron concentration</th>
<th>Iron concentration</th>
<th>Iron concentration</th>
<th>Iron concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Dextran</td>
<td>50 mg/ml</td>
<td>50 mg/ml</td>
<td>50 mg/ml</td>
<td>50 mg/ml</td>
</tr>
<tr>
<td>LMW Iron Dextran</td>
<td>50 mg/ml</td>
<td>50 mg/ml</td>
<td>50 mg/ml</td>
<td>50 mg/ml</td>
</tr>
<tr>
<td>Total dose infusion (TDI)</td>
<td>Up to 500 mg</td>
<td>Up to 500 mg</td>
<td>Up to 500 mg</td>
<td>Up to 500 mg</td>
</tr>
</tbody>
</table>

LMW Iron Dextran (InFeD, Cosmofer)

- Iron Dextran was on backorder, now available
- We did carry the 50 mg/ml x 2 ml vial - cost $15.50/100mg vial
- Iron dextran 50mg elemental iron/mL (IM or IV)
  - Self-limiting infusion reactions < 1%
  - Serious adverse events < 1:200,000
- Total dose infusion — LMW iron dextran may be given as a total dose infusion (TDI)
- Test dose
Iron Sucrose (Venofer, iron saccharate)

- We do have iron sucrose 20mg/ml x 5ml vial - cost $37.50/100 mg vial, we do have stock
- Iron sucrose — 20 mg iron/mL is only approved for IV use.
- Unlike other formulations, iron sucrose cannot be administered as a total dose infusion
  - doses above 300 mg are not recommended
- Test dose
  - No need for test dose in product-naive patients
  - test dose is recommended (25 mg by slow IV push) in patients who are sensitive to iron dextran or have other drug allergies.

Ferric gluconate (Ferrlecit)

- Available with no restrictions (12.5mg/ml x 5 ml amp)
- cost $33.60/125mg dose
- Ferric gluconate is approved for a maximum single dose of 125 mg (IV only)
  - diluted and infused over 20 to 30 minutes.
  - It can also be administered as a 125 mg two-minute bolus in dialysis patients.
  - remainder of the calculated dose of iron is given at subsequent treatment sessions at this rate
- Test dose —
  - No need for a test dose in product-naive patients
  - recommended in patients with iron dextran allergy

Ferumoxytol (Feraheme)

- Currently available
  - 30mg/ml x 17ml vial = 510mg/vial
  - cost $196.90/510mg vial
- Contraindication if other medication allergies
- Superparamagnetic iron oxide nanoparticles coated with a low molecular weight semisynthetic carbohydrate
  - Rapid IV infusion 510 mg of elemental iron over 17 sec in patients CKD and dialysis or over 30 min
  - may transiently affect the diagnostic ability of MRI
  - Notify radiologist if infusion given within 4 weeks of MRI
Conclusions

- Iron deficiency syndromes are common
- Important to distinguish iron deficiency from anemia of chronic disease
- Intravenous iron is safe and effective
  - Hepcidin – therapeutic target for future therapies in inflammatory anemia