

## Update on iron deficiency and supplementation

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## Faculty Disclosures

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- Faculty: Sarah Robbins
- Relationships with commercial interests
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  - Other: none

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## Objectives

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

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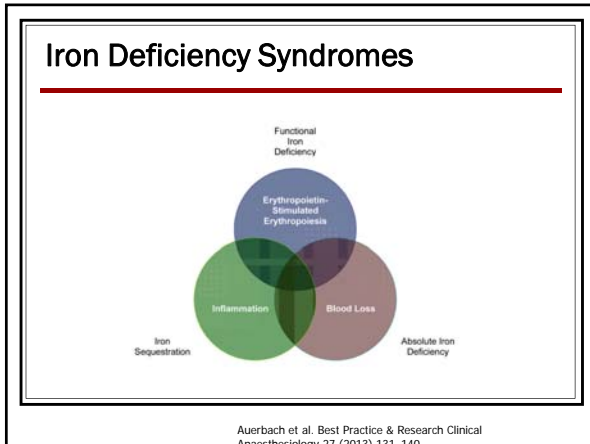
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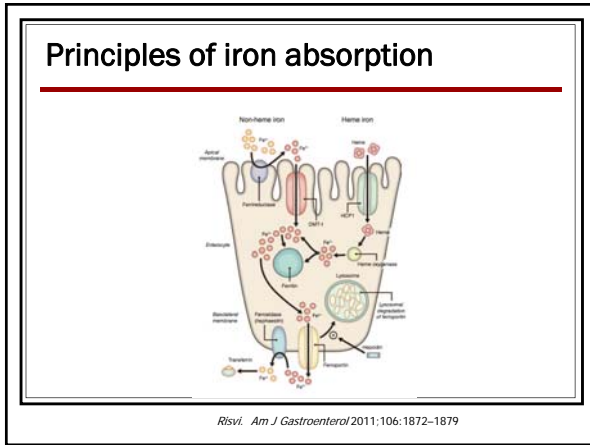
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- ### Iron Deficiency Symptoms
- **Anemia**
    - Reduced performance, fatigue
    - Headache
    - Dizziness
    - Tachycardia, dyspnea
  - **Non-hematological**
    - Hair loss
    - Paresthesia of hand and feet
    - Restless leg syndrome
- Stein & Dignass. Ann Gastro 2013; 26: 104 - 113

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## Laboratory Findings in Anemia

**Table 3. Serum Levels That Differentiate Anemia of Chronic Disease from Iron-Deficiency Anemia.\***

Variable	Anemia of Chronic Disease	Iron-Deficiency Anemia	Both Conditions†
Iron	Reduced	Reduced	Reduced
Transferrin	Reduced to normal	Increased	Reduced
Transferrin saturation	Reduced	Reduced	Reduced
Ferritin	Normal to increased	Reduced	Reduced to normal
Soluble transferrin receptor	Normal	Increased	Normal to increased
Ratio of soluble transferrin receptor to log ferritin	Low (<1)	High (>2)	High (>2)
Cytokine levels	Increased	Normal	Increased

NEJM 2005

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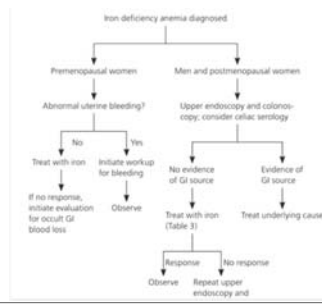
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## Approach to Iron Deficiency Workup




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## Anemia of Chronic Disease

Associated Diseases	Estimated Prevalence* percent
Infections (acute and chronic)	18-95 <sup>10,11</sup>
Viral infections, including human immunodeficiency virus infection	
Bacterial	
Parasitic	
Fungal	
Cancer†	30-77 <sup>12-14</sup>
Hematologic	
Solid tumor	
Autoimmune	8-73 <sup>15,16,18</sup>
Rheumatoid arthritis	
Systemic lupus erythematosus and connective-tissue diseases	
Vasculitis	
Sarcoidosis	
Inflammatory bowel disease	
Chronic rejection after solid-organ transplantation	8-30 <sup>17,18</sup>
Chronic kidney disease and inflammation	23-50 <sup>19,20</sup>

NEJM 2005

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## Oral Iron Absorption

### Oral iron absorption

#### A. Effectors of iron absorption

Inhibiting iron absorption	Facilitating iron absorption
<ul style="list-style-type: none"> <li>Coffee, tea, milk, cereals, dietary fiber, phosphate-containing carbonated beverages</li> <li>Multivitamin or dietary supplements containing calcium, zinc, manganese or copper</li> <li>Antacids, H2 blockers and proton pump inhibitors</li> <li>Quinolones and tetracycline antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>Vitamin C</li> <li>Acidic foods e.g. tomato sauce</li> <li>Non enteric coated iron tablets</li> <li>Fasting ingestion of iron supplements</li> </ul>

#### B. Oral iron absorption test<sup>8</sup>

<b>Step 1:</b> Measure morning serum iron level (baseline).
<b>Step 2:</b> Ingest approximately 60mg elemental iron (324 mg ferrous sulfate) with water.
<b>Step 3:</b> After 1-2 hours, measure the serum iron level.
<b>Step 4:</b> Compare the serum iron levels.
<b>Interpretation:</b> An increase in serum iron of >100 µg/dl suggests that absorption is generally adequate.

Alleyne et al. Am J Med 2008; 12(111): 943 - 948

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## Bivalent versus trivalent iron

Table 1: Differences between bivalent and trivalent oral iron preparations.

Iron supplement	Comments
<b>Bivalent</b>	
Ferrous fumarate (Fe <sup>2+</sup> )	
Ferrous gluconate (Fe <sup>2+</sup> )	More adverse effects if not in a prolonged-release formulation
Ferrous sulphate (Fe <sup>2+</sup> )	
Ferrous glycinic sulphate (Fe <sup>2+</sup> )	
<b>Trivalent</b>	Poorer absorption
Iron protein succinylate (Fe <sup>3+</sup> )	More expensive
Iron polymaltose complex (Fe <sup>3+</sup> )	A greater number of intakes

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

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## Comparison of Oral Iron Formulations

Formulation	Brand Name	% Elemental Iron (w/w)	Dosage Form	Information
Ferrous fumarate	Palifer	33	Tablets; chewable tabs	
Ferrous gluconate	Floradix	12	Tablets	
Ferrous sulfate	Fer-In-Sol; Ferodan	30	Oral elixir; Tablets; Enteric coated tablets	
Heme iron polypeptide	Proferrin	100	Capsules	Hgb extracted from bovine RBC
Polysaccharide iron complex	Triferexx	100	Capsules; solution	Ferric iron complexed to hydrolyzed starch

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## Iron Replacement Dose Estimates

A. Estimated total oral dose of elemental iron for anemia correction. Additional dosing cycle(s) of 5000mg may be required to replenish iron stores.

Hemoglobin (g/dl)	Elemental Iron Total dose (mg)*
> 11	5000
9-11	10,000
< 9	15,000

B. Calculation based upon total blood volume and hematocrit (Hct)

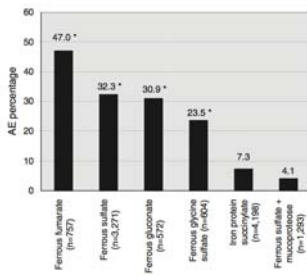
Total iron deficit = iron stores deficit + Hemoglobin iron deficit  
 Iron stores deficit = 500-1000 mg  
 Hemoglobin iron deficit = body wt (kg) x (target Hb - actual Hb)  
 Target Hb 14 g/dl.

Oral elemental iron replacement estimate (mg) = 10 x total iron deficit

\* assuming 10% absorption, 60 kg patient.

Alleyne et al. Am J Med 2008; 12(111): 943 - 948

## Tolerability of Oral Iron



Cancelo-Hidalgo Curr Med Res & Opin 2013;29 (4):291-303

## Relative Cost of Iron Formulations

Iron preparation	Brand name	Recommended dose	Cost
<b>Oral iron</b>			
Ferrous sulfate	Fascol, Fer-Gen-Sol, Fer-in-Sol, Fer-ion	325 mg (65 mg elemental iron) three times a day	\$2.50 (100-tablet bottle)
Ferrous gluconate	Fergen	325 mg (36 mg elemental iron) three times a day	\$8.56 (100-tablet bottle)
Ferrous fumarate	Ferriox, Ferrilets, Ferro-Sequin, Neopro Fer	324 mg (106 mg elemental iron) three times a day	\$10.98 (100-tablet bottle)
<b>IV iron</b>			
Iron sucrose	Venclor	100 mg elemental iron (cumulative dose of 1 g over 14-28 days)	\$688 for 10 doses
Iron dextran	Dexferum Infil	0.0442 (desired hemoglobin-observed hemoglobin) x lean body weight (in kg x 0.25 x lean body weight)	\$450 for 1 dose \$372.04 for 1 dose
Ferri gluconate	Ferriject	125 mg elemental iron (total of 8 doses for cumulative dose of 1 g)	\$381.60 for 8 doses
Ferumoxytol	Feraheme	510 mg elemental iron (total of 2 doses for cumulative dose of 1 g)	\$476.14 for 1 dose \$4,761.36 for 10 doses

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

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### 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

Cook. Best Prac & Res Clin Haematol 2005;18(2):319-332

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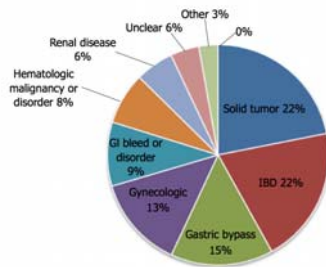
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### Indications for IV Iron – Miami Experience



Warsch et al. 2013

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### 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

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

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### Intravenous iron preparations

	Iron dextran (LMW)	Iron gluconate	Iron sucrose	Iron carboxymaltose	Ferumoxytol	Iron isomaltoside
Molecular weight	165 kD	37.5 kD	45.3 kD	150 kD	731 kD	150 kD
Complex stability	High	Low	Moderate	High	High	High
Test dose required	Yes	No	Yes	No	No	No
Maximum approved dose	20 mg/kg BW	62.5 mg	200 mg* 7 mg/kg BW	1000 mg if patient weight > 66 kg 15 mg/kg b	510 mg	20 mg/kg BW
Maximum infusion period	300 min	30 min	210 min	15 min	17 sec	15 min
Maximum single dose on injection	200 mg	62.5 mg	200 mg	500 mg	510 mg	200 mg
Minimum infusion period	2 min	10 min	10 min	bolus	17 sec	bolus
Dose-related reactions	Hypotension, edema	Hypotension, edema	Hypotension, edema	None reported	None reported	None reported
Relative risk of severe side effects	Moderate	Low	Very low	None reported	Very low	None reported
Costs per 500 mg (€)**	84-86	52-56	105-110	170-175	***	170-175

\*In most countries the dose is fixed to 200 mg (10ml), in some countries 500 mg are approved  
 \*\* in Germany August 2012  
 \*\*\* approved by the EMA in April 2012, but not yet available  
 LMW low molecular weight

Stein & Dignass. *Annals of Gastroenterology* (2013) 26, 104-113

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### 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

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### 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-naïve patients
  - test dose is recommended (25 mg by slow IV push) in patients who are sensitive to iron dextran or have other drug allergies.

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### 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-naïve patients
  - recommended in patients with iron dextran allergy

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### Ferumoxitol (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

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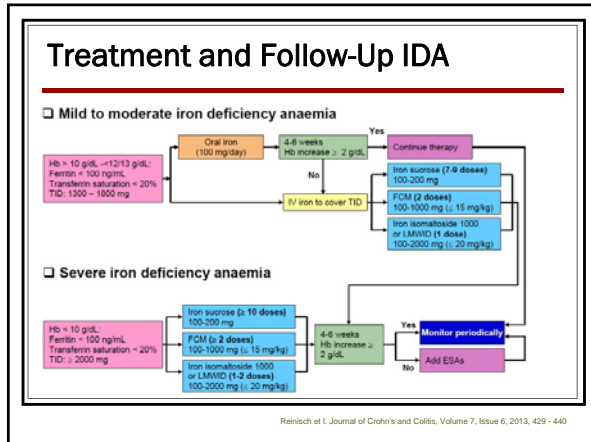
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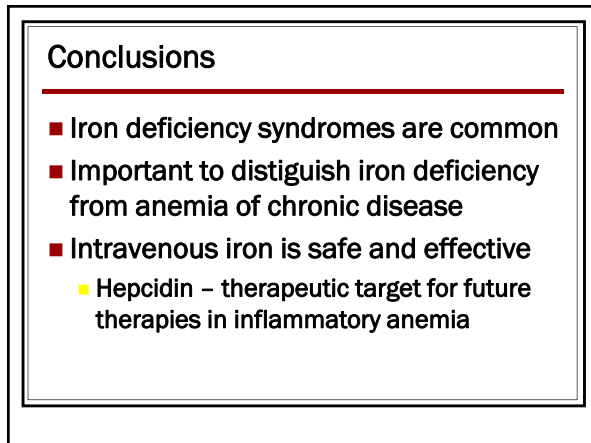
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