Iron Deficiency Anemia in Primary Care

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June 1st, 2021

Objectives

- Identification of Iron Deficiency (ID) and Iron Deficiency Anemia (IDA)
- Impact of IDA on health
- Investigation of the Underlying ETIOLOGY
- Review oral and intravenous (IV) iron repletion
  - Appropriate dosing strategies
  - Adverse effects

Prevalence of IDA

- Most common cause of anemia worldwide, affecting over one billion people, predominantly woman and children

US National Health and Nutrition Examination Survey (NHANES) from 2003-2010:

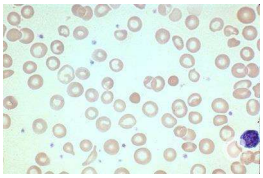
- 15% toddlers
- 11% adolescent girls
- 9% adult woman (age 20-49)

Nutrition Impact Model Study estimated global prevalence of anemia in pregnancy 38% in 2011

Stevens GA et al. Nutrition Impact Model Study. Lancet Glocal Health. 2013;1(1):e16-e25.

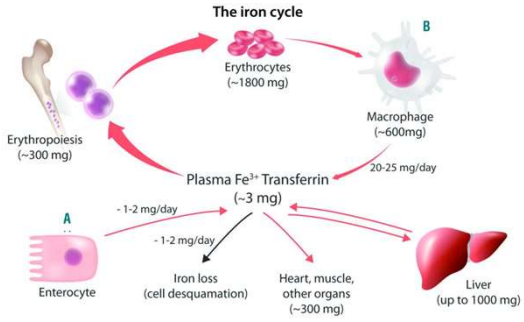
Iron Deficiency Stages

- Total body iron stores are reduced (low ferritin), even with normal CBC and MCV
- *Note retics can be increased initially if bleeding, but will decrease as iron stores depleted*



As iron stores are exhausted:

- Microcytic (MCV <80)
- Hypochromic (pale, MCHC)
- Anemic (Hgb decreased)



Wcamaschella C. et al. Haematologica. 2020;105(2):260-272.

Diet

- Typical Western diet contains ~10 to 20 mg of iron
- Inorganic iron (cereals, legumes) and heme iron (red meats, fish, poultry)
- Inorganic iron is less readily absorbed then heme iron
- Calcium rich foods, tannins in tea, coffee, anti-acids decrease iron absorption
- Absorbic acid increases absorption

Table 1
Iron Sources in Food

Meats*	Size (oz.)	Iron (mg)
Veal liver	1	4-5
Beef	3	4-5
Lamb	4	4-5
Ham	2	1.5-2
Chicken	3-4	1.5-2
Bologna	3-4	1.5-2
Fruits, grains, vegetables†	**Quantity/Size**	**Iron (mg)**
Raisins	0.5 C	4-5
Peas, cooked	0.5 C	2-4
Beans, cooked	0.5 C	2-4
Figs	3 medium	2-4
Barley	0.5 C	1.5-2
Oatmeal	1 C	1.5-2
Beans, green	1 C	1.5-2
Rice	1 C	0.7-1.4
Potato	1 medium	0.7-1.4

**The body can absorb up to 40% of iron in these foods.*
†The body can absorb 10% or less of iron in these foods.
C, cup.
Source: Reference 12.

Saljoughian M. et al US Pharmacist. 2007;32(8):HS26-HS37.

Patient Case 1

- 43 yo woman with no significant PMH presents for fatigue and dyspnea on exertion after her regular weekly run over last few weeks
- Heavy menses that began last few years with more irregular cycles
- Changes pads q2 hours, waking through night to change pads, passing large clots and leaking through clothes
- Denies other bleeding history (gum bleeding, epistaxis, melena, hematuria)
- Supplements: not on PPI Surgeries: w/o bleeding complications
- Diet: not vegan

Patient Case 1

- Exam: pale conjunctivae, otherwise NAD
- CBC: WBC 8.1, Hgb 6.5 g/dL, MCV 65 (previously normal couple years ago), plts 572k. CMP wnl
- Additional history, lab or imaging evaluation?
- History: historic CBCs, recent viral infections, ETOH, liver dx
- Labs: P smear, retics 0.6%, RDW 15.7%, ferritin 4 ng/mL, iron sat 3%
  Historic CBCs are useful
- Imaging: Pelvic US

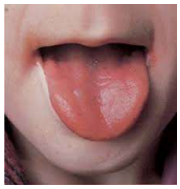
Presenting Features

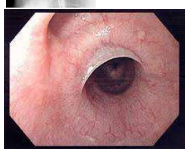
- Symptoms of anemia: fatigue, weakness, headache, irritability, depression, decreased exercise tolerance
- Pica (clay, dirt, rocks, starch, chalk, paper, cardboard, raw rice)
- Pagophagia (craving ice)
- Koilonychia (spoon nails)
- Restless leg syndrome

- Angular cheilitis
- Atrophic glossitis
- Impaired memory, concentration, cognitive development

Plummer-Vinson Syndrome

- Dysphagia (esophageal webs)
- Atrophic glossitis
- Iron deficiency





IDA and Cognitive Effects

- **Executive Functioning:** n=127 woman age 18-35 year old; better iron status associated with better attention, planning ability (Scott SP et al. J Nutr. 2016)
- **Perception, attention, memory:** n=126 woman, consumed ferrous fumarate; significant improvement in perception, attention, mnemonic function related to change in blood iron markers ($p<0.05$; Wenger MJ et al. J Nutr. 2017)
- **Academic performance:** n=105 woman age 18-35 yo; GPA was higher in woman with normal compared with low ferritin ($p=0.01$; Scott SP et al. J Nutr. 2017)
- **Infant development:** longitudinal studies consistently indicate that children anemic in infancy continue to have poorer cognition, school achievement and more behavioral problems into middle school (Grantham S. et al,. J Nutr. 2001)

Confirming the Diagnosis

- Serum ferritin is the most reliable initial test *(Correlates with the body's iron stores in the absence of inflammation)*
- Ferritin less than 30 ug/L achieves a high sensitivity (92%) and high specificity (98%) for diagnosis of ID
- Ferritin 1 ug/L = ~8 to 10 mg tissue iron

- Inflammatory conditions may "normalize" ferritin *(Acute phase reactant)*
- Low transferrin saturation (Tsat) less than 20% plus a higher ferritin threshold of less than 100 ug/L can be used for diagnosis of ID in setting of inflammation

Confirming the Diagnosis

- Serum iron (Fe) level and TIBC are unreliable indicators of iron availability to the tissues because of wide fluctuations in levels resulting from recent ingestion of dietary iron

- *If want an accurate serum Fe then need to do a fasting serum Fe!*

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Differential Diagnosis of IDA

	Iron deficiency	Thalassemia trait	Inflammation
MCV	Low in proportion to anemia (may be nl in early stage)	Low even in absence of anemia	Normal or slightly low
Serum iron	Low	Normal	Low
TIBC	High	Normal	Normal or low
Serum ferritin	Low	Normal	Normal or high
Marrow iron	Absent	Present	Present

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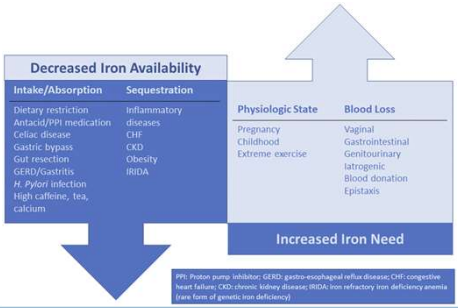
Etiologies of IDA



Shuoyan Ning,Michelle P. Zeller, Management of iron deficiency, Hematology Am Soc Hematol Educ Program, 2019, Figure 2.

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Patient Case 1

- PCP sent to emergency room for severe anemia (Hgb 6.5 g/dL)
- Given patient's stability, ED physician held off on pRBC transfusion
- Received single dose of high-dose, short-infusion-time IV iron
- Prescribed oral iron with instructions for administration
- Referred to GYN to evaluate cause of HMB
- Close followup with PCP to ensure adequate Hgb recovery

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Choosing Wisely

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Five Things Physicians and Patients Should Question

1 **Don't transfuse more units of blood than absolutely necessary.**

Each unit of blood carries risks. A restrictive threshold (7.0-8.0g/dL) should be used for the vast majority of hospitalized, stable patients without evidence of inadequate tissue oxygenation (evidence supports a threshold of 8.0g/dL in patients with pre-existing cardiovascular disease). Transfusion decisions should be influenced by symptoms and hemoglobin concentration. Single unit red cell transfusions should be the standard for non-bleeding, hospitalized patients. Additional units should only be prescribed after re-assessment of the patient and their hemoglobin value.

2 **Don't transfuse red blood cells for iron deficiency without hemodynamic instability.**

Blood transfusion has become a routine medical response despite cheaper and safer alternatives in some settings. Pre-operative patients with iron deficiency and patients with chronic iron deficiency without hemodynamic instability (even with low hemoglobin levels) should be given oral and/or intravenous iron.

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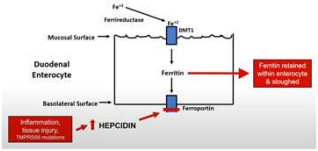
Oral Iron

- Inexpensive, available in resource poor settings
- Effective in most patients w/ classic IDA, if taken
- *GI side effects common limiting factor, ~30 - 60%*
- *Requires 3 to 6 months of therapy*

- Do not give with food
- Gastric acidity is helpful
- Ferrous best absorbed (Fe++)
  - Ferrous sulfate



- Ineffective if significant inflammatory block

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Oral Iron

Drug class	Example	Dose per tablet (mg)	Elemental iron content per tablet (mg)	Dose	Special instructions
Iron salts	Ferrous gluconate	240	27	1-3 tablets, once per day or once every other day	Take on empty stomach; consider vitamin C; take at a different time of day than antacid or proton pump inhibitor. Acidic environment required.
		325	38		
	Ferrous sulfate	325	65	1-2 tablets, once per day or once every other day	
	Ferrous fumarate	325	106	1 tablet, once per day or once every other day	
Heme iron polypeptide	Proferrin	398	11	1-3 tablets per day	Can be taken with a meal. Acidic environment not required for absorption.
Polysaccharide iron complex	Feramax	150	150	1 tablet once per day	Can be taken with a meal. Acidic environment not required for absorption.
Ferric citrate	Auryxia	210	210	3-5 tablets once per day	Can be taken with a meal. Acidic environment not required for absorption.

Shuoyan Ning,Michelle P. Zeller, Management of iron deficiency, Hematology Am Soc Hematol Educ Program, 2019, Table 2.

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Every Other Day Oral Dosing

- 2015 study of 54 woman were given various doses of iron that contained traceable isotope to track absorption; iron absorption was best when restricted to lower doses (40-80 mg elemental Fe no more than once a day); higher or more frequent doses of iron raised hepcidin and reduced subsequent fractional iron absorption
- 2017 study of 40 woman randomly assigned to ferrous sulfate 60 mg once daily x 14 days vs every other day for 28 days (same cumulative dose); every other day resulted in greater absorption (131 vs 175 mg total); trend decreased nausea

Moretti D et al, Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice daily doses in iron depleted young woman, Blood, 2015, 126(17):1981-9.
Stoffel NU et al. Iron absorption from oral iron supplements given on consecutive vs alternate days and as single morning doses vs twice daily split dosing in iron depleted woman. Lancet Haematol. 2017; 4(11):e524.

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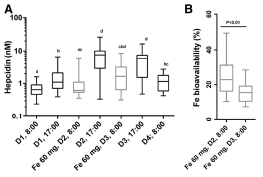
Every Other Day Oral Dosing

Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women.



Diego Moretti,Jeroen S. Goede,Christophe Zeder,Markus Jiskra,Vaiya Chatzinakou,Harold Tjalsma,Alida Melse-Boonstra,Gary Brittenham,Dorine W. Swinkels,Michael B. Zimmermann, Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women, Blood, 2015, Figure 3

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Side Effects

- Common in all formulations
- GI (nausea, constipation, diarrhea, vomiting, metallic taste, and dark stool)
- Dose-dependent
  - Enteric coated reduces absorption (release too far in the intestine), so has lower GI toxicity
  - Supplements with lower amounts of elemental iron has lower GI toxicity
- Improve tolerability
  - *Every other day dosing**
  - *Liquid, easier to titrate the dose*

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Patient Case 1

- Seen in followup 2 weeks after ED visit
- Reports unable to tolerate oral iron due to constipation
- CBC shows 2 weeks after IV iron shows Hgb 9.1 g/dL
- What is adequate replacement therapy for remaining IDA?
- Retic count should increase in one week after iron started
- Hemoglobin should increase in two weeks after iron started
- How to calculate residual iron deficit?

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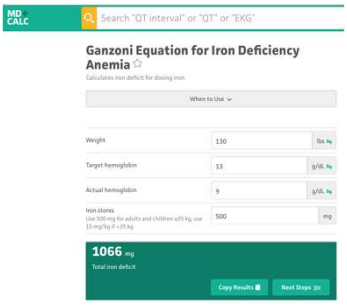
Ganzoni Iron Deficit Calculator



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IV Iron

Compound	Brand name	Recommended amount per dose	Infusion time	Availability	Reference
Low-molecular-weight iron dextran	INFeD	100 mg after uneventful 25-mg test dose	2-6 h (+ test dose)	United States, Europe	https://www.pdr.net/drug-summary/INFeD-iron-dextran-2087; https://www.allergan.com/assets/pdf/infed_pi
Ferrous gluconate	Ferrlecit	125 mg	12.5 mg/min	United States, Europe, Canada	http://products.sanofi.us/ferrlecit/ferrlecit.html
Iron sucrose	Venofer	200-300 mg	100 mg/30 min	United States, Europe, Canada	http://www.venofer.com/Indications_Dosage
Ferumoxytol	Feraheme	510 mg	15 min	United States, Europe	https://www.feraheme.com/dosing-and-administration/
Ferric carboxymaltose	Injectafer	750 mg	15 min	United States, Europe	https://injectaferhcp.com/iron-deficiency-anemia-dosing
	Ferinject	1000 mg	15 min	United States, Europe	https://www.ferinject.co.uk/simplified-dosing-for-all-patients/
Iron isomaltoside	Monofer	≤1000 mg	>15 min	United States, Europe	https://www.medicines.org.uk/emc/files/pil.5676.pdfinu

Shuoyan Ning,Michelle P. Zeller, Management of iron deficiency, Hematology Am Soc Hematol Educ Program, 2019, Table 3.

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IV Iron

- Stability of the iron-carbohydrate complex (carbohydrate shell) that bind iron determines amount of iron safely delivered in single infusion
  - You can give higher single dose of iron dextran (InFed 1000 mg over 1to 4 hours) and ferric carboxymaltose (Injectafer 750 mg over 15 min) because they are more stable than ferric gluconate (Ferrlecit 125 mg-250 mg over 1-2 hours) and iron sucrose (Venofer 200-300 mg over 90 min)
- Excessive doses result in free iron release, which can result in the hypersensitivity ("pseudo-allergy") reactions

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IV Iron

- IV iron used for unresponsiveness to or intolerance of po iron
- IV iron used if rapid replacement is desired (severe anemia or preoperative)
- Choice of IV iron formulation may be guided by what is available at your institution, covered by insurance, etc
- Severe hypersensitivity reactions and anaphylaxis are rare

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IV Iron Replacement Example

Ex. Hgb 8 g/dL, 70 kg = 2200 mg deficit

IV iron allows full repletion in few infusions depending on the product
-FCM (Injectafer) 750 mg (3 infusions)
-Iron sucrose (Venofer) 200 mg (10 infusions)

Maximum oral absorption is ~25 mg/day (~90 days)

Auerbach M. et al, J Lab Clin Med, 1988; McEvoy GK et al., Am Society Health System Pharm, 1995

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Patient Case 1

- Insurance preferred iron sucrose – 300 mg x 4 infusions (total 1200 mg)
- GYN evaluated and found fibroid; plans low-dose progesterone IUD
- CBC shows one month after IV iron shows Hgb 11.1 g/dL
- What is ongoing replacement therapy for prevention of IDA?
- If using oral iron continue to replenish iron stores for 3 months after hemoglobin normalizes..
- Or as long as ongoing bleeding
- How often to recheck CBC, iron studies? ~q3 to 6 months

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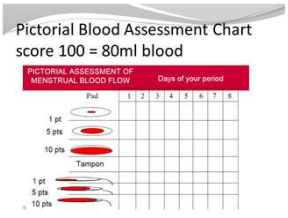
Heavy Menstrual Bleeding

- **ACOG:** bleeding lasting >7 days and/or loss of >80 mL blood/menstrual cycle
  - PBAC score
- **IFGO:** excessive menstrual blood loss that interferes with woman's physical, emotional, social and material QOL



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Low-dose progesterone IUD

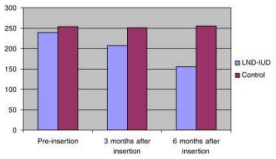

Fig. 1. PBAC scores of the groups versus time (p value is significant at the third and sixth months).

LNG-IUD safe even in woman with prior VTE and effective at decreasing PBAC scores in woman on anticoagulation

Kilic S et al., Contraception, Aug 2009

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Patient Case 11

- 72 year old man w/ A fib on apixaban presents to PCP c/o dyspnea on exertion & fatigue
- CBC: WBC 6.1, Hgb 7.4 g/dL (baseline 14 g/dL), MCV 74, plts 502k, and retic count 1%
- Ferritin 9 ug/L w/ low serum iron and elevated TIBC
- What is most common source of iron deficiency in men and post-menopausal woman?
  - GI bleeding source found in 60%; GI malignancy in ~10-15%
- Next steps: EGD and colonoscopy negative; followed by capsule study which showed small bowel angiodysplasia

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Occult Sources of IDA

- Refractoriness to oral iron defined as Hgb increment <1 g/dL after 4 to 6 weeks of therapy at daily dose of ~100 mg elemental iron

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Occult Sources of IDA

- *In study 2005, refractoriness found in 100% celiac disease, 69% autoimmune gastritis, and 68% H pylori infection*

Diagnosis	Autoimmune gastritis	*H pylori**	Menorrhagia	Gastrointestinal lesions	Celiac	Negative
n (%)	77 (26)	57 (19)	96 (32)	31 (10)	14 (5)	21 (7)
Mean age ± 1 SD, y	41 ± 16	37 ± 19	39 ± 10	60 ± 14	39 ± 14	33 ± 13
Gender, M/F	14/63	17/40	0/96	13/18	3/15	2/21
Main diagnosis alone	26	57	39	21	11	21
H pylori	39	—	57	10	2	0
Menorrhagia	11	0	—	0	1	0
Gastrointestinal lesions	1	0	0	—	0	0
Aspirin or NSAID	9	3	1	7	0	1
Refractory to oral iron, %	69	68	38	47	100	10

Hershko C and Clara Camaschella, How I treat unexplained refractory iron deficiency anemia, Blood, 2013, Table 1.

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Occult Sources of IDA

- Consider work-up for unexplained or refractory IDA:
  - Confirm not blood donor
  - Repeat GI bleeding evaluation
  - Urine-analysis for microscopic hematuria
  - Confirm no epistaxis, other sources of bleeding
  - H pylori stool antigen, urease breath test or gastroscopy w/ biopsies
  - Serum gastrin, anti-parietal and anti-intrinsic factor antibodies
  - Celiac screen with serology (TTG IgA antibodies) or duodenal biopsy
  - If childhood iron deficiency or strong family history, genetic testing (TMPRSS6) for iron-refractory iron deficiency anemia (IRIDA)

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Patient Case 11

- Hold apixaban anticoagulation until GI bleeding evaluated/treated
- Iron deficit ~1500 mg
- Receives IV Ferric carboxymaltose (Injectefer) 750 mg x 2 infusions
- S/p argon laser treatment of angiodysplasia
- Echocardiogram: mild aortic stenosis
- A followup 3 months later shows Hgb normalized 13.8 g/dL

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Questions

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