Pulling Back the Iron Curtain: Iron Deficiency Anemia Pearls and Potions

PRESENTED BY: Marie Hogan, MD, Assistant Professor, OHSU Department of Pediatrics, Division of Hematology/Oncology

DOERNBECHER CHILDREN'S Hospital
OHSU

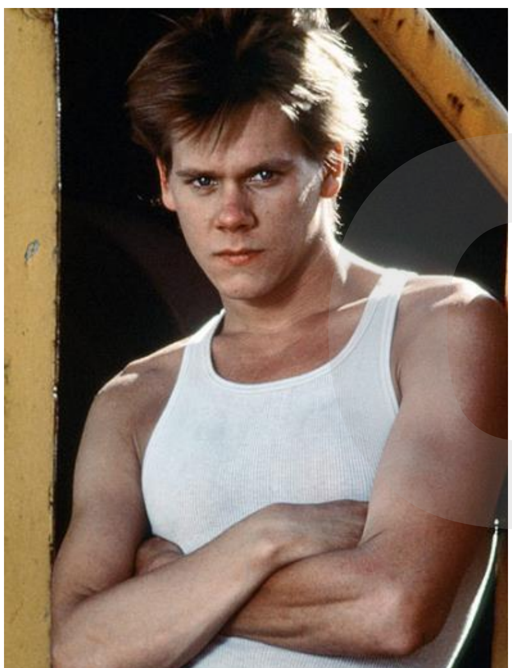
Disclosure Information:

a) Moderators/panelists/presenters: Marie Hogan has nothing to disclose.

Learning Objectives:

1) List the laboratory findings of iron deficiency and iron deficiency anemia
2) Describe the non-hematological effects of iron deficiency and iron deficiency anemia
3) Identify indications for IV iron and discuss the risks and benefits of IV iron

Iron content of bacon:
0.1 mg per slice



Iron content of Kevin Bacon:
4 g

“Gold has its uses, but war is won with iron.”

- George R.R. Martin

Iron containing proteins*

Heme Proteins	Iron-dependent Enzymes
Hemoglobin	Aldehyde oxidase
Myoglobin	Reduced nicotinamide adenine dinucleotide dehydrogenase
Cytochrome a, b, c	Tyrosine hydroxylase
Cytochrome P-450	Succinate dehydrogenase
Tryptophan-1,2-dioxygenase	Prolyl hydroxylase
Catalase	Xanthine oxidase
Myeloperoxidase	Ribonucleotide reductase
	Aconitase
	Phosphoenolpyruvate carboxykinase

*adapted from Nathan and Oski Hematology
*not a complete list

Iron: pretty important

"Human existence is inextricably linked to iron, and disturbances in its metabolism may have dire consequences."

-Nancy Andrews, Christina Ulrich, and Mark Fleming

- The key to the utility of iron is that it can exist in either of two stable oxidation states:
  - Fe^{2+} (Ferrous)
  - Fe^{3+} (Ferric)
- This allows iron to act as a redox catalyst – reversibly donating or accepting electrons

Iron: untamed

- Iron + aqueous solution = ferric iron
- Ferric iron is insoluble at physiologic pH → ferric hydroxide salts = rust
- To prevent formation of insoluble ferric iron, iron must be complexed with chelators (i.e.: transferrin)

Iron: untamed

"Unbound iron has unbridled redox activity…"

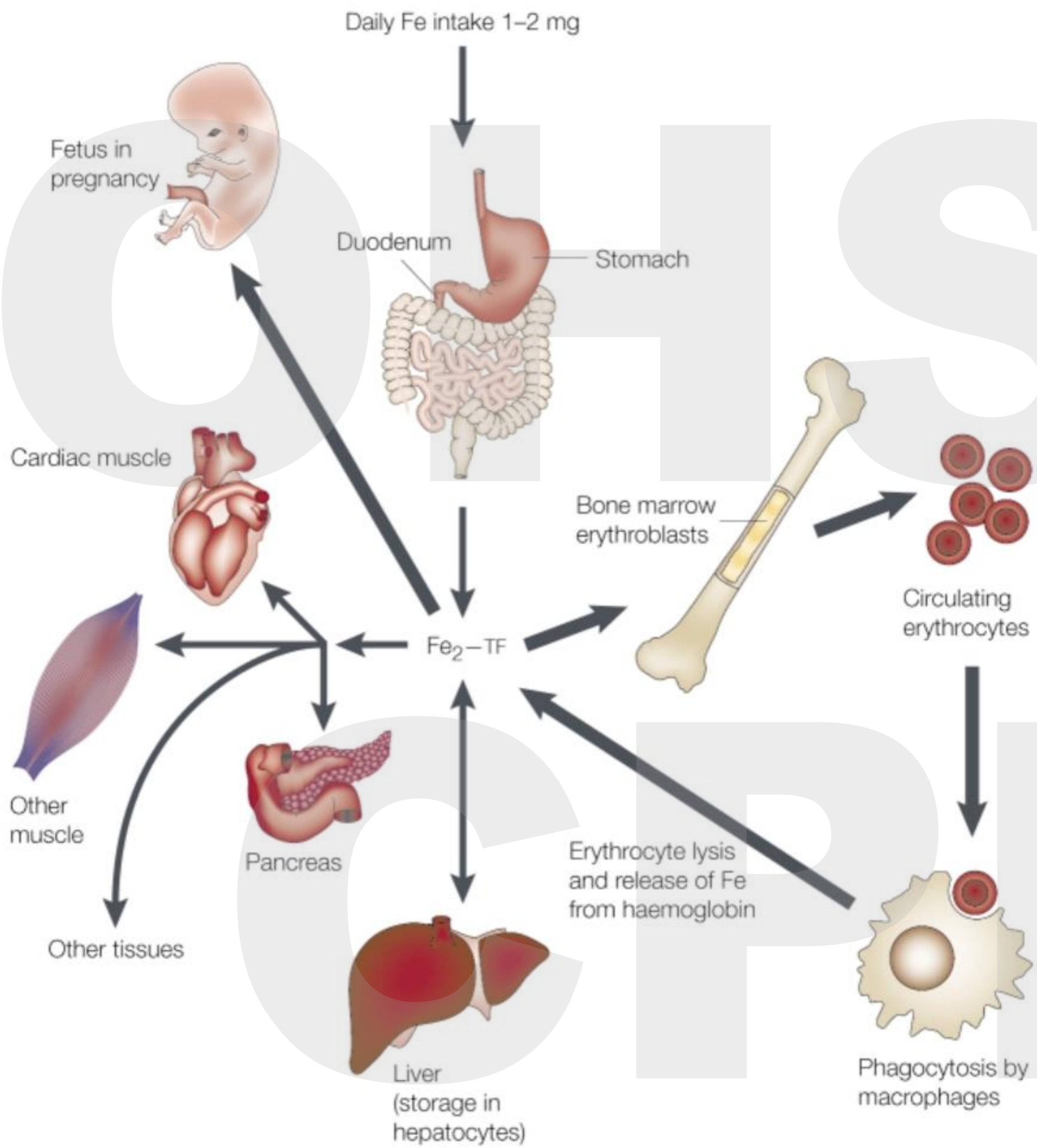
-Nancy Andrews, Christina Ulrich, and Mark Fleming

- Reactive oxygen intermediates are converted to free radicals by iron-catalyzed reactions
- Hydroxyl radicals promote peroxidation of membrane lipids and result in leaky lysosomes and cell death
- Iron can be present in cell membranes in sickle cell disease and thalassemia – contributing to pathogenesis

http://diehardbrain.blogspot.com/2012/03/free-radicals-and-antioxidants.html

Iron chelators: Minimizing iron reactivity

- Transferrin
  - 90 kD serum glycoprotein
  - Binds 2 iron atoms with very high affinity
  - Carries iron through the circulation
  - Delivers iron to cell transferrin receptors
- Ferritin
  - Stores iron within cells
  - Holds up to 4500 iron atoms (4500!!!)
  - Iron can be mobilized when needed



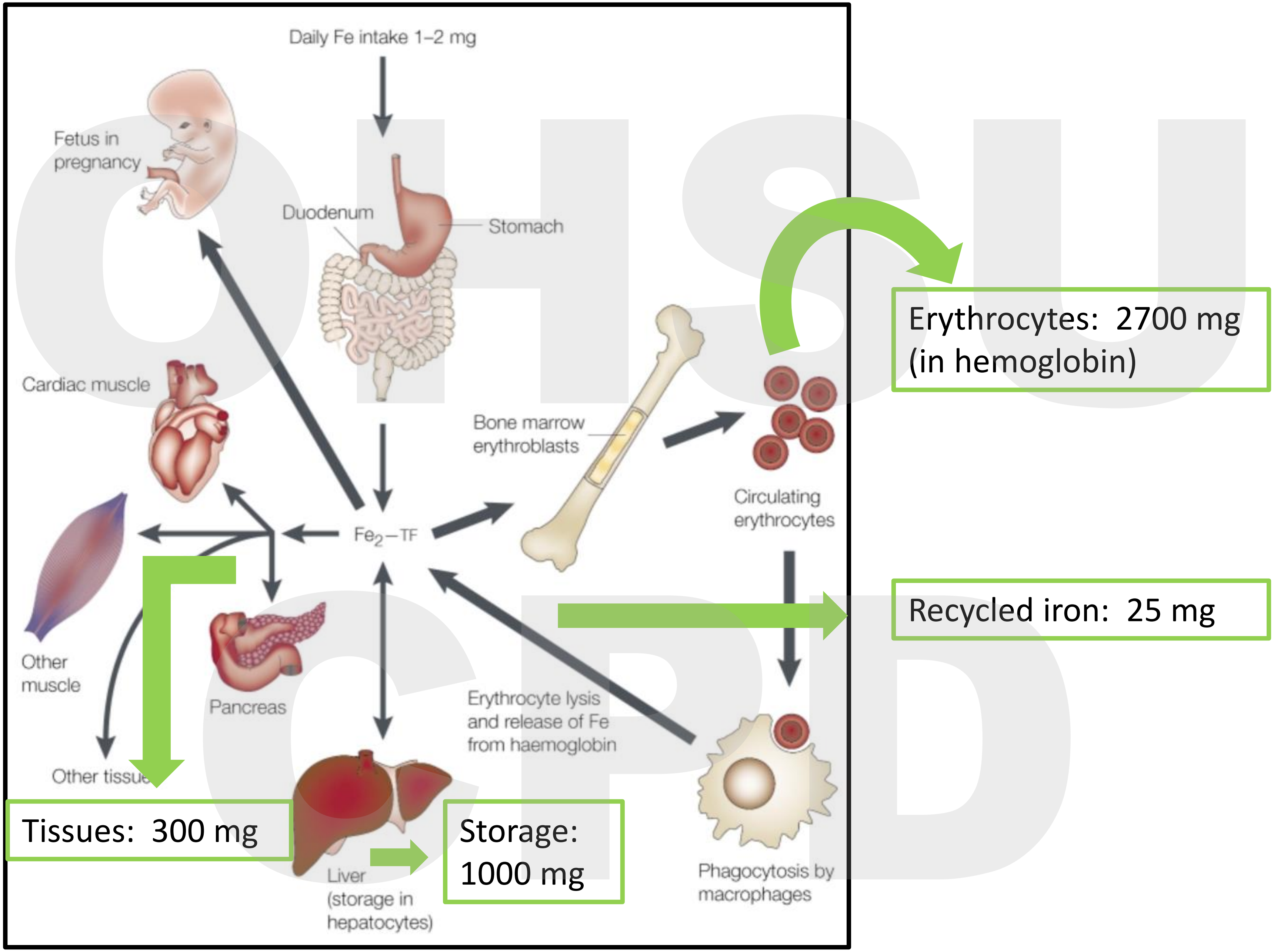
Iron Economy:
The average adult (Kevin Bacon included) has 4-5g of body iron.

Only ~1-2 mg of iron enters and leaves the body in a day on average.

About 0.5-1 mg of iron is lost each day through sloughing of cells (skin and mucosal surfaces)

About 1 mg of iron is lost daily in menstruating women.

Adapted from Andrews NC Nat Rev Gen 2000 (1): 208-217 and Nutritional Anemias by Matthew Heeney, ASPHO review course

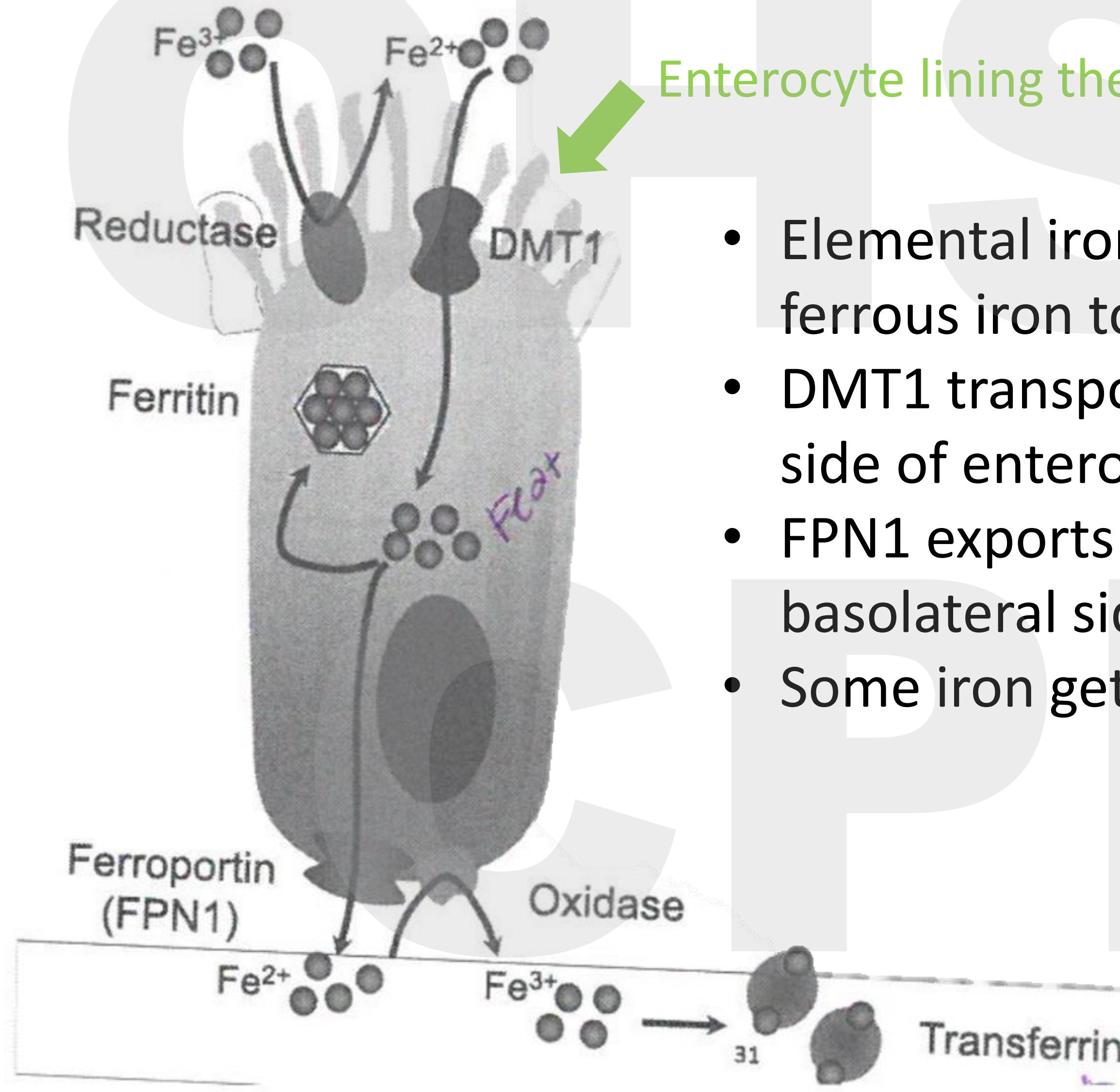


Adapted from Andrews NC Nat Rev Gen 2000 (1): 208-217 and Nutritional Anemias by Matthew Heeney, ASPHO review course

Iron balance – maintained by regulation of absorption

- Absorption:
  - Regulated by intestinal uptake
  - Uptake can be increased up to 10x normal
  - Responsive to iron status, erythropoietic demand, hypoxia, inflammation
- Loss:
  - Unregulated
  - Sloughing of cells – skin and mucosa
  - Bleeding
  - Pregnancy

Intestinal iron absorption



Enterocyte lining the duodenal villi

- Elemental iron must be reduced to ferrous iron to be absorbed
- DMT1 transports iron at the apical side of enterocytes
- FPN1 exports ferrous iron at the basolateral side to transferrin
- Some iron gets stored in ferritin

Image from Mark D Fleming, MD, Dphil- ASPHO review course

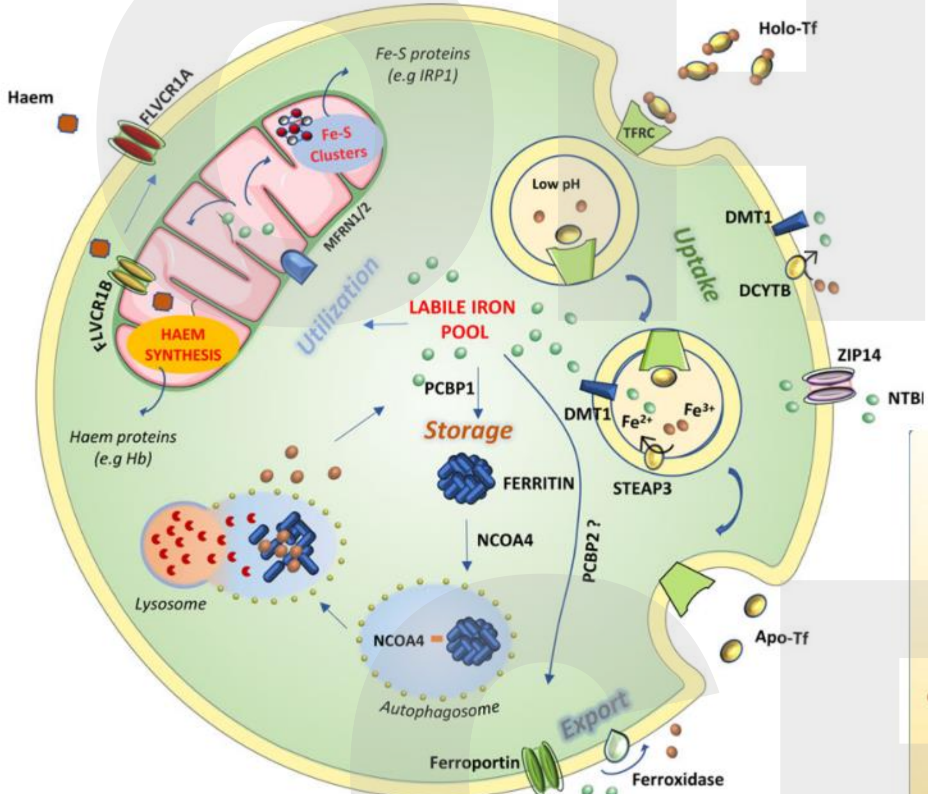
Intestinal iron absorption

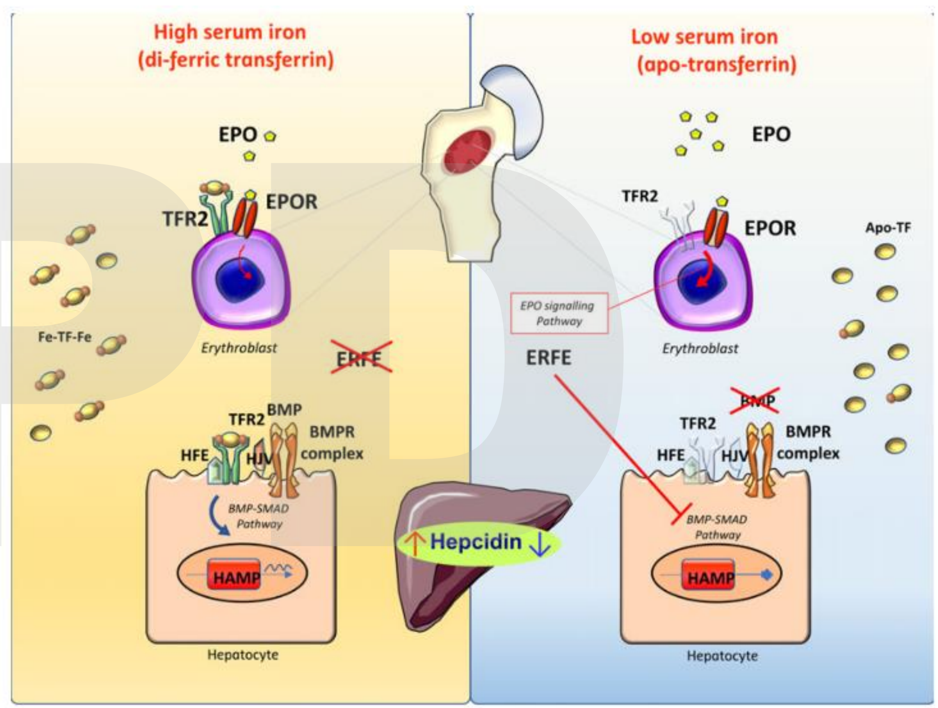
- Heme iron: the iron found in meat, poultry, and fish (blood and muscle)
- Non-heme iron: plant foods e.g. vegetables, legumes, and nuts
- Heme iron absorption is much better (30-70%) than non-heme iron absorption (<5%)
- Mechanism of heme iron absorption is still unknown!

Intestinal iron absorption

Helps ☺	Hinders ☹
Red meat	Vegetable fiber
Ascorbic Acid	Phytates
Breast milk	Phosphates
Iron deficiency	Tea/Tannin
	Cow's milk
	Antacids

Iron metabolism in depth





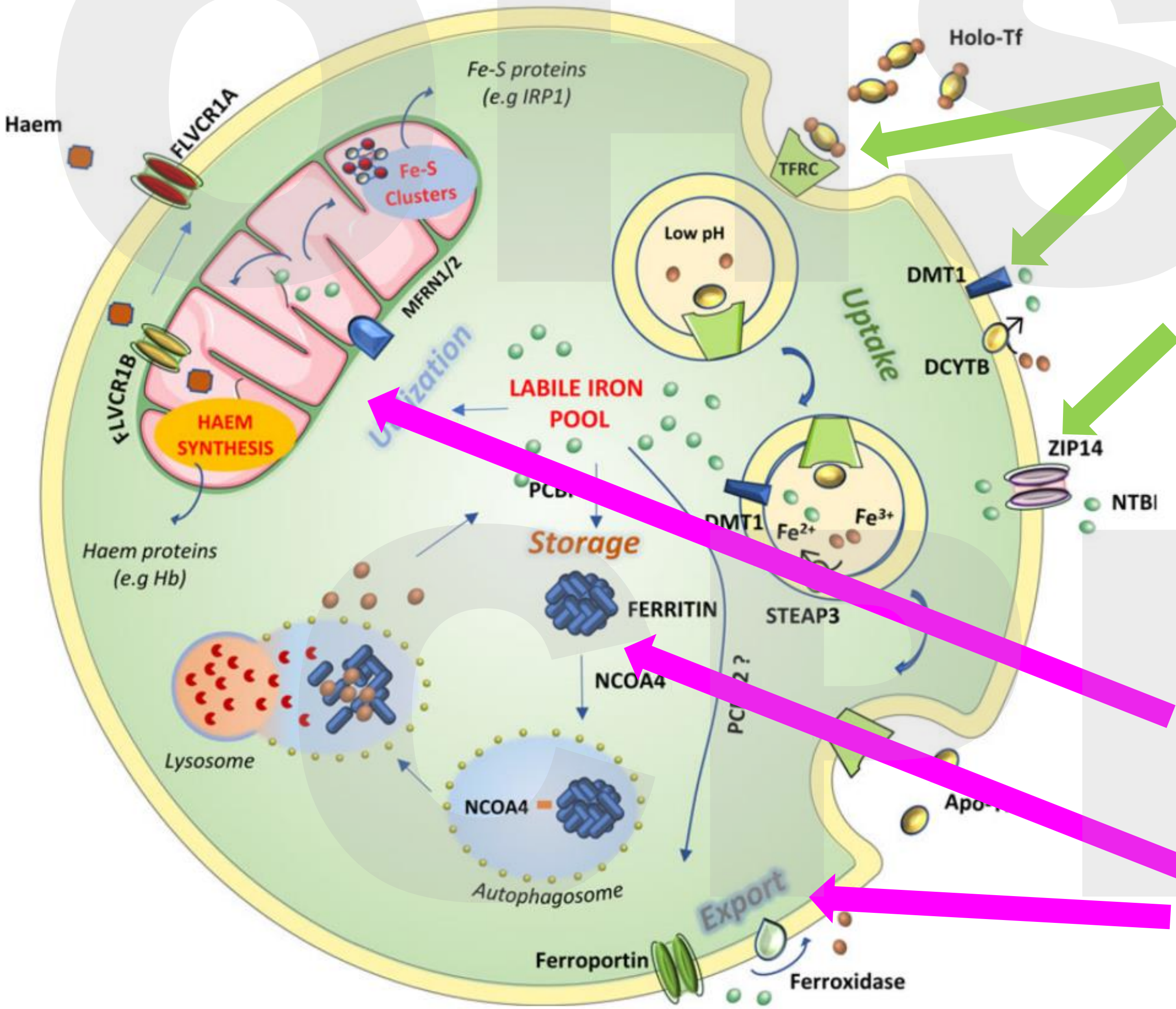
Camaschella C and Pagani A. BJH. 2018 (182): 481-494.

Do one thing every day that scares you.

-Eleanor Roosevelt

Hancock, Noelle (2011-05-07). *My Year with Eleanor: A Memoir* (Kindle Locations 162-163). HarperCollins. Kindle Edition.

Iron trafficking



Transferrin receptor (TFRC) and the Divalent metal transporter 1 (DMT1) import iron

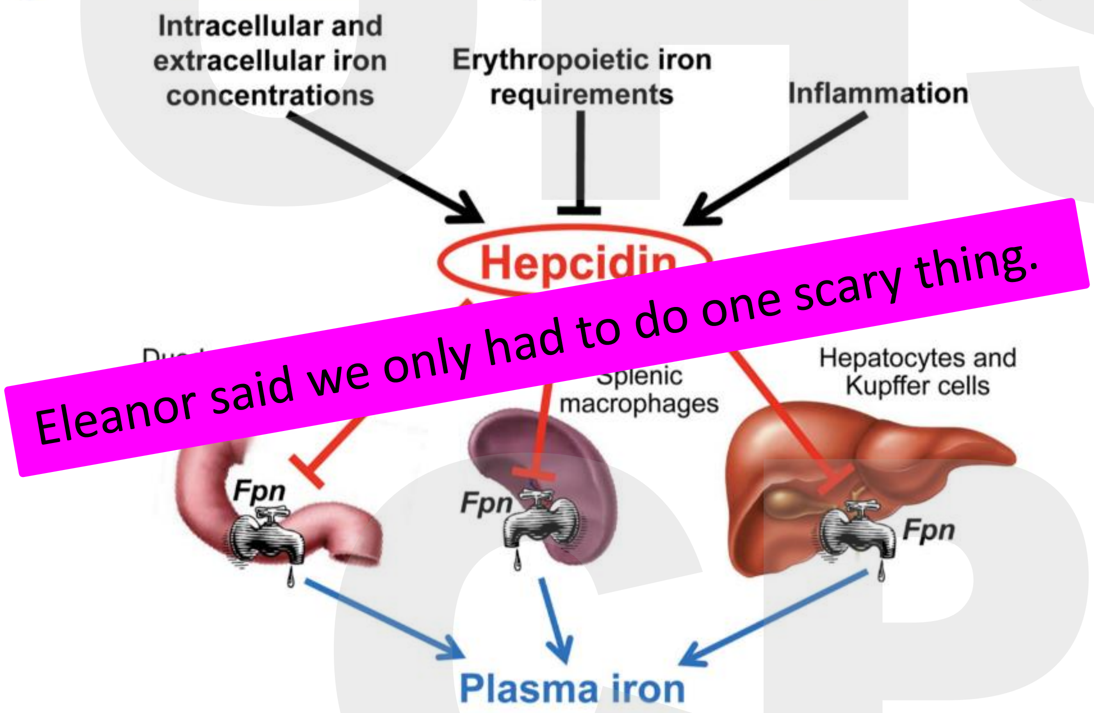
Zinc transporter protein (ZIP14) takes up iron in iron overload states

Once inside, iron joins the labile iron pool. It is then either

1) Utilized in mitochondria for protein production;
2) Stored in ferritin
3) Exported through ferroportin

Camaschella C and Pagani A. BJH. 2018 (182): 481-494

Systemic iron regulation: Hepcidin

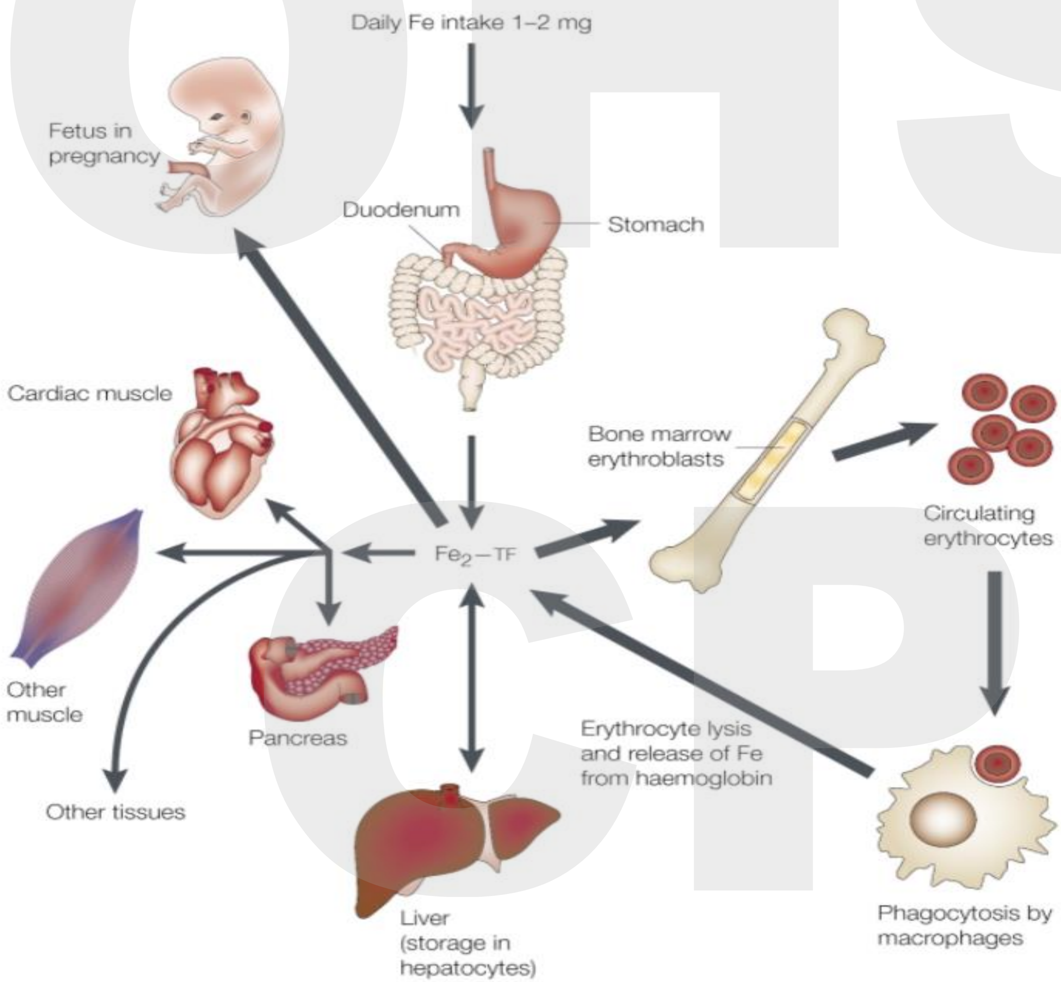


Ganz T and Nemeth E. Biochim Biophys Acta. 2012 (9): 1434-14

Camaschella C and Pagani A. BJH. 2018 (182): 481-494

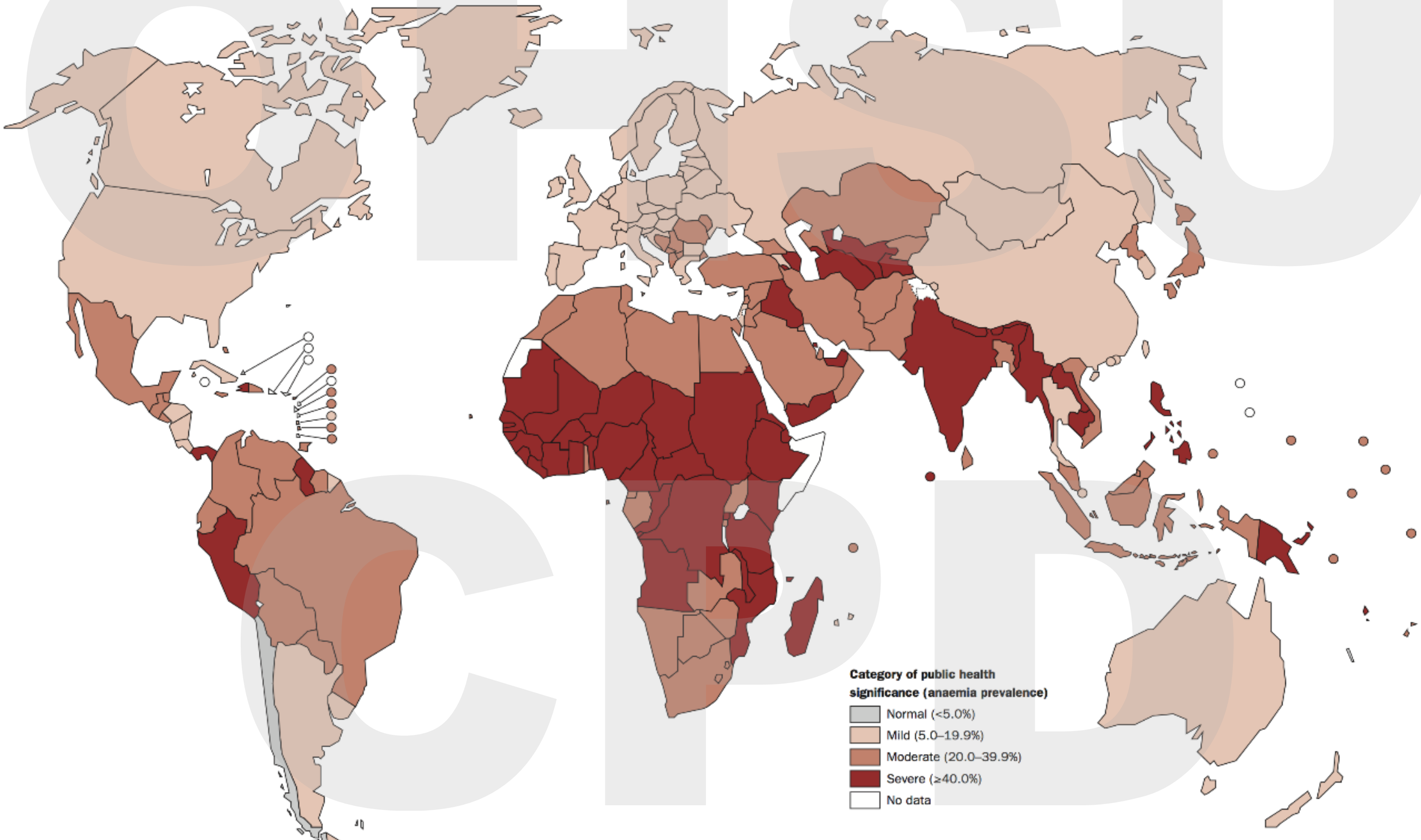
- Hepcidin is a negative regulator of iron export
- Hepcidin inhibits intestinal iron absorption
- Hepcidin inhibits macrophage iron release
- If your body needs more iron, Hepcidin decreases
- If your body needs less iron, your Hepcidin increases

Iron economy: iron deficiency



- Not enough in
- Too much out
- Inadequate absorption
- Dysfunctional iron metabolism

Iron deficiency: epidemiology



Non-pregnant women of reproductive age

WHO global database on Anaemia – 1993-2005

Looker A, et al. JAMA 1997 277(12):973-976

Iron deficiency: signs/symptoms

Substances Ingested By Patients With Pica and Iron Deficiency*

Form of Pica	Substance	References
Amylophagia	Starch	3-14
Cautopyreiophagia	Matches	15, 16
Coniophagia	Dust from venetian blinds	This report
Geomelophagia	Potatoes	17, 18
Geophagia	Clay, dirt	1, 3-11, 19-39
Gooberphagia†	Peanuts	40
Lectophagia	Lettuce	1, 20, 41-44
Lithophagia	Stones, pebbles, rocks	15, 23, 39, 45
Pagophagia	Ice	5, 10, 20, 37, 41, 42, 47-52
Stachtophagia	Ashes from cigarettes	3, 46, 53, This report
Trichophagia	Hair	54, 55
Xylophagia	Wood toothpicks	This report

- Cardiac murmur (10%)[7]
- Tachycardia (9%)[8]
- Neurocognitive dysfunction
- Angina pectoris
- Vertigo

Rare

- Haemodynamic instability (2%)[8]
- Syncope (0·3%)[9]
- Koilonychia
- Plummer-Vinson syndrome (<0·1%)[10]

Often, iron deficiency (even severe) is asymptomatic in pediatric patients

Iron deficiency: etiology

Not enough in:

- Insufficient intake to meet physiologic needs – especially those who are rapidly growing
- Cow’s milk – has minimal iron (<1 mg/L), iron is not bioavailable, the milk fills you up, and it may cause GI bleeding via microtrauma

Iron deficiency: etiology

Too much out:

- GI blood loss (gastritis, ulcers, parasites, varices, IBD, etc.)
- Recurrent prolonged epistaxis (check for bleeding disorders)
- Heavy menstrual bleeding (check for bleeding disorders)
- Hematuria (chronic infections)
- Pulmonary losses (pulmonary hemosiderosis)

Iron deficiency: etiology

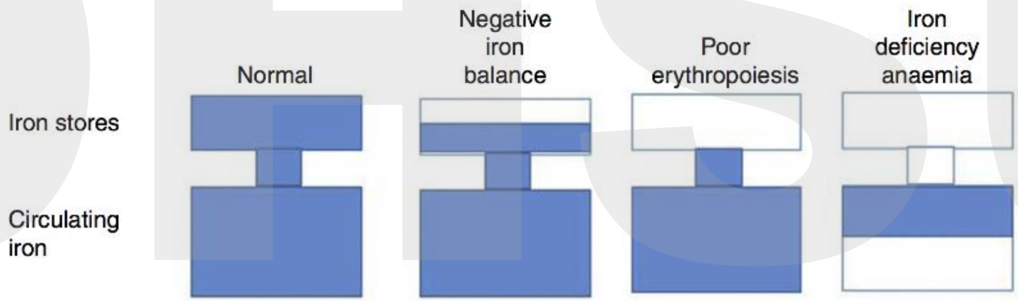
Inadequate absorption:

- Celiac disease (1 in 31 patients with IDA have celiac)
- Prior bowel resection
- Inflammatory bowel disease
- Iron Refractory Iron Deficiency Anemia (IRIDA) (mutations in TMPRSS6)

Iron deficiency: labs

- CBC: microcytic, hypochromic anemia
    - Lower limit of normal hemoglobin: 11 + [0.1 x (age in years)]
    - Lower limit of normal MCV: 70 + [1 x (age in years)]
- Smear: microcytosis, poikilocytosis, anisocytosis, cigar cells
- Ferritin ↓
- TIBC ↑
- Transferrin saturation ↓
- Serum iron ↓ ⟳ ↑

Iron deficiency: labs



	Normal	Negative iron balance	Poor erythropoiesis	Iron deficiency anaemia
Stored in bone marrow	1-3+	0-1+	0	0
Serum ferritin mcg/dl	50-200	<20	<15	<15
TIBC mcg/dl	300-360	>360	>380	>400
Serum iron g/dl	50-150	NL	<50	<30
Saturation (%)	30-50	NL	<20	<10
Protoporphyrin mcg/dl	30-50	NL	>100	>200
Morphology	NL	NL	NL	Microcytic/ hypochromic

Barragan-Ibanez G, et al. Rev Med Hosp Gen Mex. 2016 (79): 88-97

Iron deficiency: labs

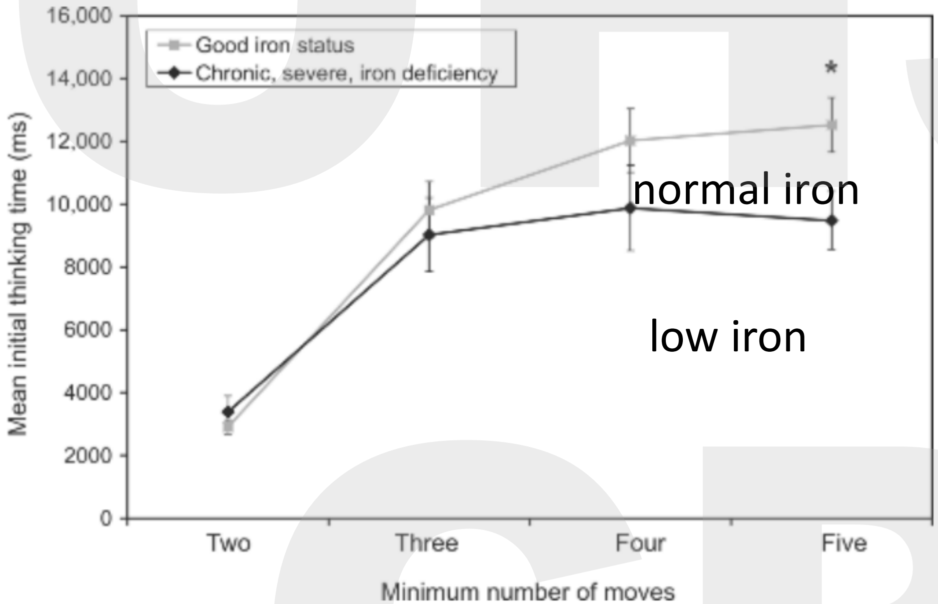
Lab	Iron Deficiency	Thalassemia	Anemia of chronic disease
Hemoglobin	Decreased or normal if early	Normal in trait, can be severely low in major	Normal to slightly decreased
MCV	Low	Very low	Low to normal
Ferritin	Decreased	Normal to Increased	Normal to Increased
TIBC	Increased	Normal	Decreased
Serum Iron	Decreased to normal	Normal to increased	Decreased to normal
Transferrin Saturation	Decreased	Normal to increased	Decreased

Other work up to consider:

- Dietary screening
- Evaluation for occult blood loss
  - Stool for blood
  - Urinalysis
  - Chest X-ray
- Celiac screening
- Bleeding disorder work up
- Hemoglobin evaluation/electrophoresis
- BMP to evaluate renal function

Iron de-“fish”-iency

Iron deficiency: non-heme effects → neuro-cognitive

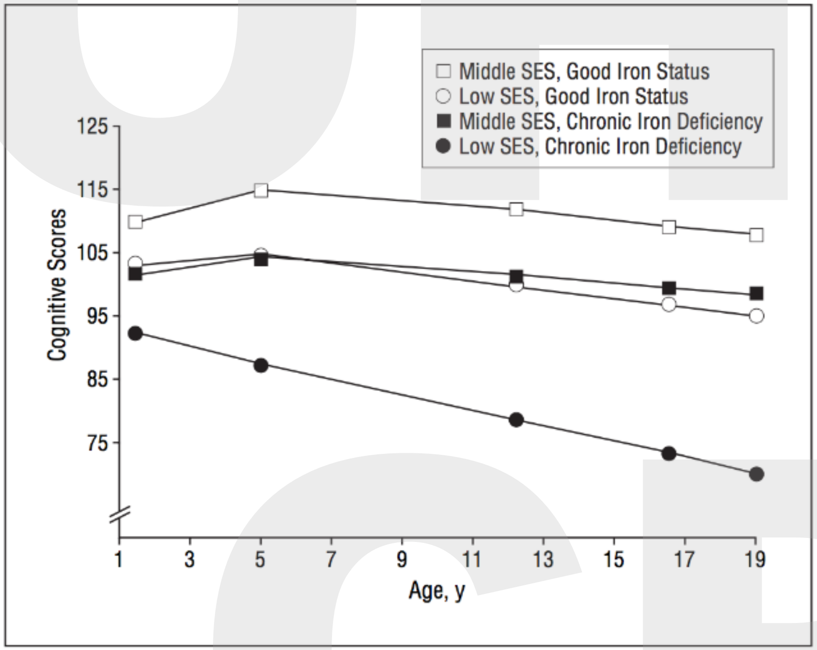


Adolescents who had been iron deficient as infants had difficulty forming and executing actions. They spent less time planning their response to the most challenging problems.

- Infants with iron deficiency anemia exhibit poor functioning in cognitive, affective, and motor domains
- Lack of sufficient iron early in life negatively impacts myelination, dendritogenesis, synaptogenesis, neuro-transmission, and neurometabolism
- These effects may be long lasting despite treatment

Lukowski, A, et al. Nutritional Neuroscience. 2013 (13):54070.

Iron deficiency: non-heme effects → neuro-cognitive

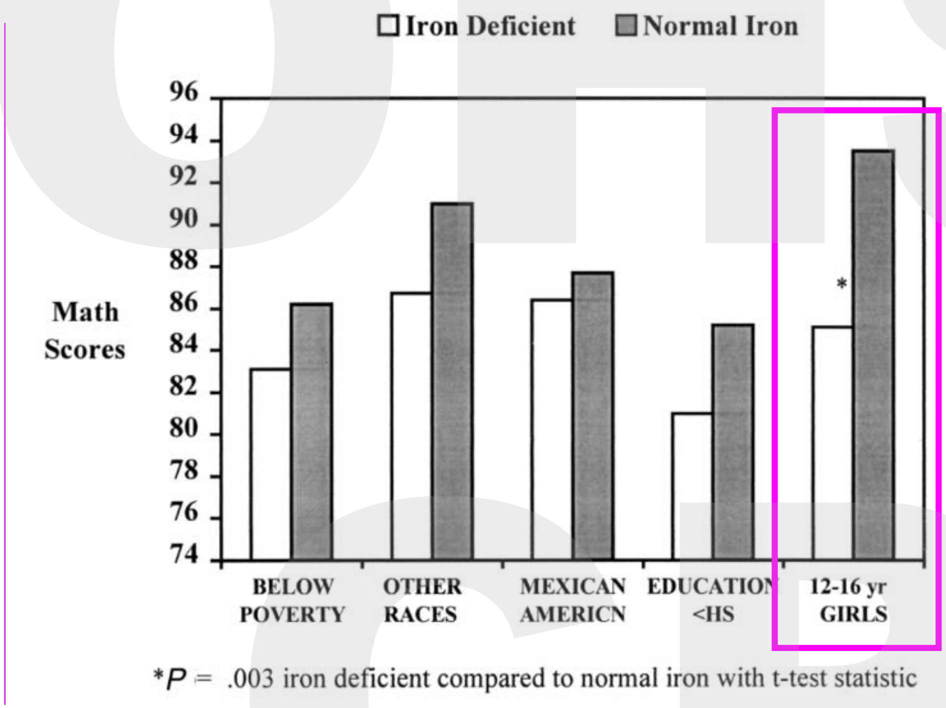


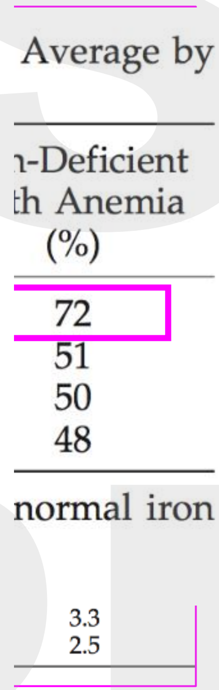
There is no evidence of catch-up in cognitive performance for individuals with chronic iron deficiency in infancy. And, there is a widening gap for those in low-SES families.

- Studies evaluating food supplementation eliminated the decline in test scores associated with low SES.
- These studies provide support for long-term cognitive benefits of improved nutrition in infancy.
- Prevention of chronic iron deficiency in infancy may have significant long term socioeconomic effects.

Lozoff B, et al. Arch Pediatr Adolesc Med. 2006 (160): 1108-1113.

Iron deficiency: non-heme effects → neuro-cognitive





- Children with iron deficiency were more than twice as likely to score below average on math tests.
- The difference in math scores was most striking in adolescent females.

NHANES data from 1988-1994, including 5398 children ages 6-16 years who completed blood work and 2 standardized tests of cognitive function. Iron deficiency was defined as ferritin < 12. Iron deficiency anemia was defined as ferritin < 12 and hemoglobin < 5% for age.

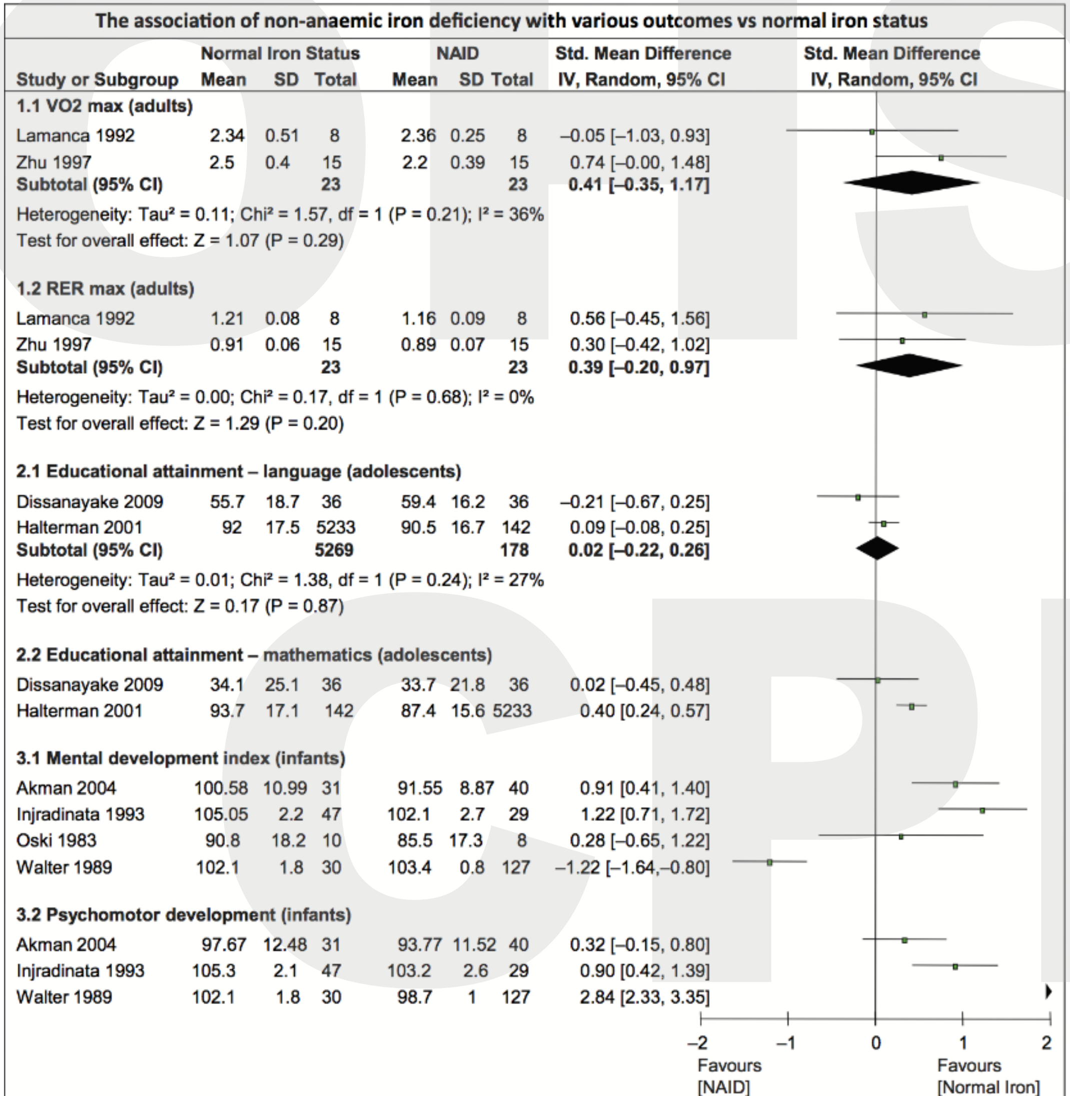
Halterman JS, et al. Pediatrics 2001 (107): 1381-1386

Iron deficiency: non-heme effects

- In women with HMB, increased health-related quality of life scores are associated with correction of anemia
- In children with iron deficiency anemia, there is a higher risk of depression, bipolar disorder, anxiety, autism, developmental delay, and attention deficit hyperactivity disorder

Peuranpaa P, et al. ACTA Obstetricia et Gynecologicia. 2014 (93): 654-660.
Chen M, et al. BMC Psychiatry. 2013 (13): 1-8.

Iron deficiency: non-heme effects



The association of non-anaemic iron deficiency with various outcomes vs normal iron status

Study or Subgroup	Normal Iron Status Mean	SD	Total	NAID Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
1.1 VO2 max (adults)							
Lamanca 1992	2.34	0.51	8	2.36	0.25	8	−0.05 [−1.03, 0.93]
Zhu 1997	2.5	0.4	15	2.2	0.39	15	0.74 [−0.00, 1.48]
Subtotal (95% CI)			**23**			**23**	**0.41 [−0.35, 1.17]**
Heterogeneity: Tau² = 0.11; Chi² = 1.57, df = 1 (P = 0.21); I² = 36%							
Test for overall effect: Z = 1.07 (P = 0.29)							
1.2 RER max (adults)							
Lamanca 1992	1.21	0.08	8	1.16	0.09	8	0.56 [−0.45, 1.56]
Zhu 1997	0.91	0.06	15	0.89	0.07	15	0.30 [−0.42, 1.02]
Subtotal (95% CI)			**23**			**23**	**0.39 [−0.20, 0.97]**
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%							
Test for overall effect: Z = 1.29 (P = 0.20)							
2.1 Educational attainment – language (adolescents)							
Dissanayake 2009	55.7	18.7	36	59.4	16.2	36	−0.21 [−0.67, 0.25]
Halterman 2001	92	17.5	5233	90.5	16.7	142	0.09 [−0.08, 0.25]
Subtotal (95% CI)			**5269**			**178**	**0.02 [−0.22, 0.26]**
Heterogeneity: Tau² = 0.01; Chi² = 1.38, df = 1 (P = 0.24); I² = 27%							
Test for overall effect: Z = 0.17 (P = 0.87)							
2.2 Educational attainment – mathematics (adolescents)							
Dissanayake 2009	34.1	25.1	36	33.7	21.8	36	0.02 [−0.45, 0.48]
Halterman 2001	93.7	17.1	142	87.4	15.6	5233	0.40 [0.24, 0.57]
3.1 Mental development index (infants)							
Akman 2004	100.58	10.99	31	91.55	8.87	40	0.91 [0.41, 1.40]
Injradinata 1993	105.05	2.2	47	102.1	2.7	29	1.22 [0.71, 1.72]
Oski 1983	90.8	18.2	10	85.5	17.3	8	0.28 [−0.65, 1.22]
Walter 1989	102.1	1.8	30	103.4	0.8	127	−1.22 [−1.64, −0.80]
3.2 Psychomotor development (infants)							
Akman 2004	97.67	12.48	31	93.77	11.52	40	0.32 [−0.15, 0.80]
Injradinata 1993	105.3	2.1	47	103.2	2.6	29	0.90 [0.42, 1.39]
Walter 1989	102.1	1.8	30	98.7	1	127	2.84 [2.33, 3.35]

Systematic review of non-anemic iron deficiency:

- 21 studies include
- Meta-analysis was limited due to variation in definitions, variable study populations, variable outcome measurements, and overall low numbers.

Future efforts should focus on defining NAID and separating it from IDA.

Pratt JJ. Et al. European Journal of Haematology. 2015 (96): 618-628.

Iron deficiency

Iron economy – daily needs

Population	Iron needs per day
Male or Female 1- 3 years old	7 mg
Male or Female 4-8 years old	10 mg
Male or Female 9-13 years old	8 mg
Male 14-18 years old	11 mg
Female 14-18 years old	15 mg
Male 19 years and older	8 mg
Female 19-50 years	18 mg
Female 51 years and older	8 mg
Pregnant women	27 mg

Courtesy of Liz Adams

Iron deficiency: treatment

- Diet alone is not enough – an iron rich diet will not treat iron deficiency!
- But, creating good iron dietary habits can help prevent recurrent iron deficiency

Foods with 2 mg or more of iron/serving	Foods with 1-2 mg of iron/serving
3 ounces cooked beef or turkey	3 ounces of chicken
½ cup of beans	3 ounces of pork
½ cup of tofu	3 ounces of turkey
1 medium baked potato	3 ounces of tuna
1 cup of cooked artichoke or spinach	½ cup of seedless, packed raisins
¾ cup of instant oatmeal	1 slice of whole-wheat bread

Courtesy of Liz Adams

Iron deficiency: treatment

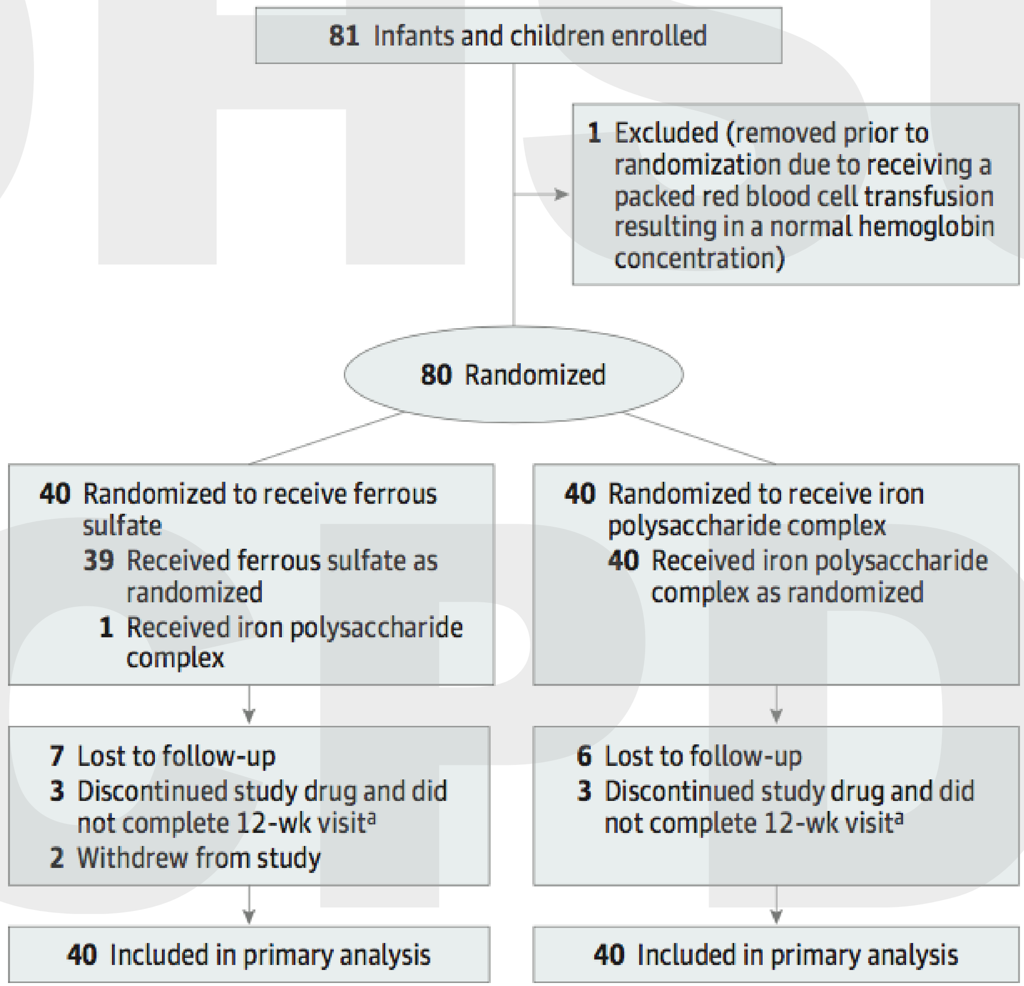
1) Correct the cause – stop bleeding, decrease milk intoxication, etc
2) Oral iron supplementation
3) IV iron supplementation

Iron deficiency: oral iron

- Previous recommendation:
  - 4-6 mg/kg/day of elemental iron in 2 divided doses for children
  - 2-3 mg/kg/day of elemental iron in 1 dose for adolescents
- Dozens of preparations exist –mostly over the counter

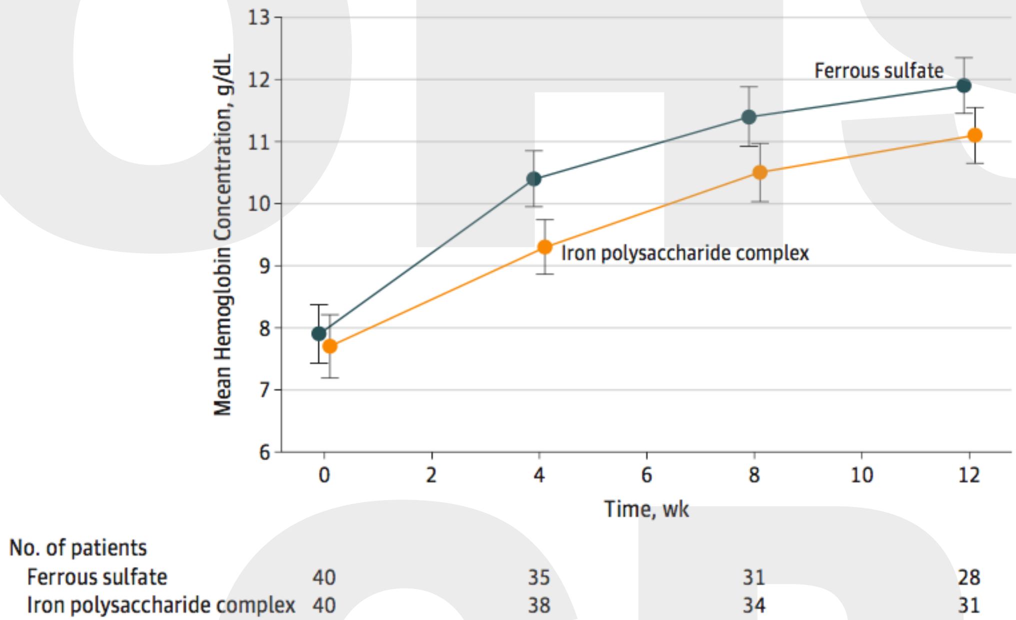
Iron deficiency: oral iron

Ferrous Sulfate 3 mg/kg day in single dose



Powers JM, et al. JAMA. 2017 (317): 2297-2304.

Iron deficiency: oral iron

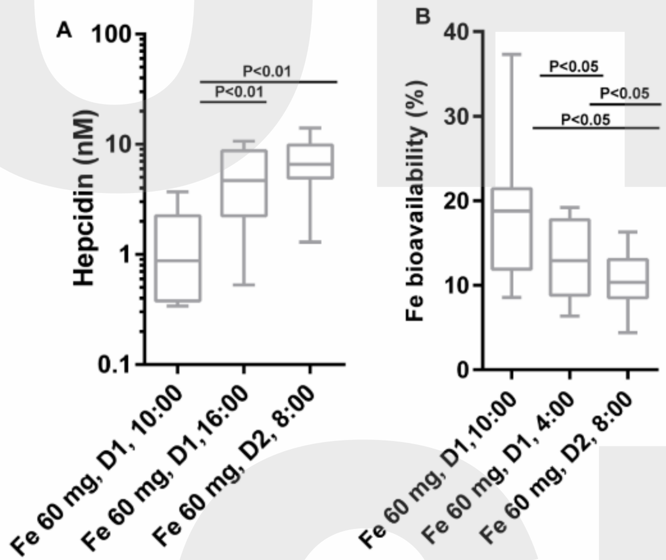


- Mean age of cohort= 23 months
- Complete resolution of iron deficiency anemia occurred in 29% of ferrous sulfate and 8% of iron polysaccharide
- Equivalent side effects in the two groups

Summary: lower dose iron is enough – 3 mg/kg/day in infants and children. Give as a single dose – no dividing.

Powers JM, et al. JAMA. 2017 (317): 2297-2304

Iron deficiency: oral iron



A complicated study of iron supplementation in women with iron deficiency but without anemia – evaluating hepcidin levels in relation to iron dosing.

Twice daily 60 mg elemental iron administration increases Hepcidin levels and decreases iron absorption.

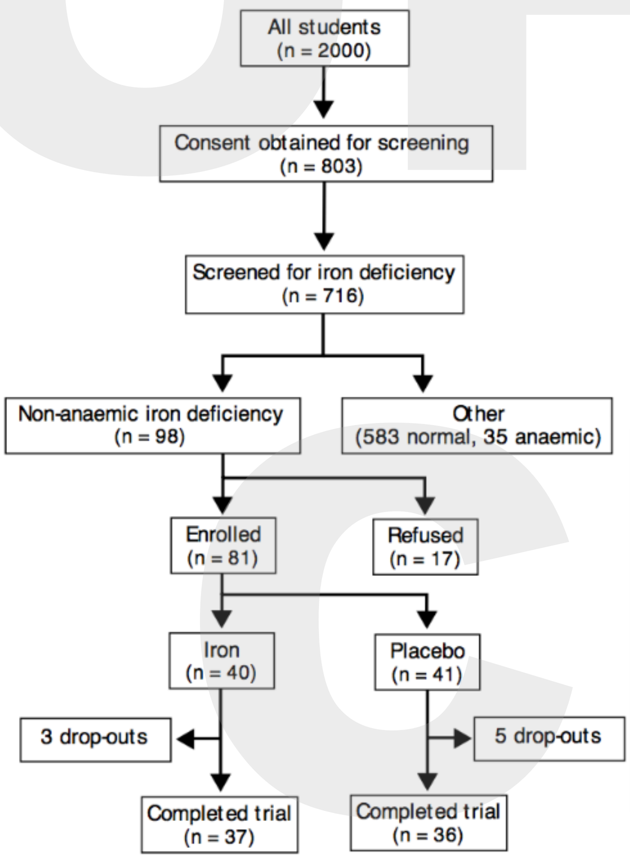
Iron deficiency: oral iron

- In infants and children: 3 mg/kg/day in a single dose
- In adolescents and young adults:65 mg elemental iron daily, or every other day
- If possible, take with heme-iron and/or vitamin C
- Do not take with
  - calcium, fiber, or antacids
  - tea (decreases absorption by 75-80%!)
  - coffee (decreases absorption by 60%!)
- Use whichever preparation results in the patient taking their iron!
  - In my back pocket: NovaFerrum, Carlson, SlowFe

Iron deficiency: response

- In 1-2 weeks after starting supplements, a reticulocytosis should be present and hemoglobin should increase by ~1 g/dL
- By 2-3 months of supplementation, anemia should be corrected
- By 4 months, stores should be replenished

Iron deficiency: non-heme treatment effects



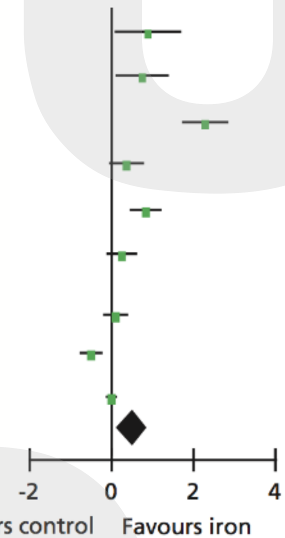
Cognitive test	R^2	R^2 change attributable to iron therapy	Baseline score	p
Attention				
SDMT	0·49	N/ A*	−0·43	0·90
VSAT	0·41	N/ A*	−1·39	0·75
BTA	0·21	N/ A*	−0·23	0·64
Learning				
HVLT	0·25	0·07	1·79	<0·02

Iron supplementation in non-anemic adolescent women improved verbal learning scores but did not affect scores on attention tests.

Bruner AB, et al. The Lancet. 1996 (348): 992-996.

Iron deficiency: non-heme treatment effects

Study	Test	Experimental			Control			SMD (95% CI)*	SMD (95% CI)*
		Mean	SD	Total	Mean	SD	Total		
Overall									
Seshadri et al.[55] (study 2)	WISC	112	14.2	14	101	9.35	14	0.89 (0.11 to 1.67)	
Gopaldas et al.[29-31]	Author-adapted scale†	25.0	5.6	32	21.3	2.32	16	0.75 (0.13 to 1.37)	
Seshadri et al.[28,55] (study 1)	WISC	118	10.5	63	95.8	7.2	34	2.29 (0.76 to 2.82)	
Seshadri et al.[28] (study 4)	Author-adapted scale†	26.0	6.19	46	23.6	6.92	55	0.37 (–0.03 to 0.76)	
Kashyap et al.[34]	Author-adapted scale†	26.5	3.55	65	23.8	2.98	65	0.84 (0.48 to 1.20)	
Soemantri et al.[56]	Raven's Progressive Matrices	98.1	6.51	71	96.5	5.82	59	0.25 (–0.10 to 0.60)	
Ayoya et al.[17]	Overall school grades	5.2	1	105	5.1	1	97	0.10 (–0.18 to 0.38)	
Sungthong et al.[57]	TONI-II	80	12	139	86	12	122	–0.50 (–0.75 to –0.25)	
Pollitt et al.[44]	Raven's Progressive Matrices	97.3	24.2	679	97.3	24.8	679	0.00 (–0.11 to 0.11)	
Total ($I^2 = 93\%$)				1214			1141	0.50 (0.11 to 0.90)	



Meta-analysis found that iron supplementation in children ages 5-12 improved global cognitive scores, IQ (in anemic children), and measures of attention. Iron also improved height in iron deficient children and weight in anemic children. Iron supplementation reduced anemia risk by 50%.

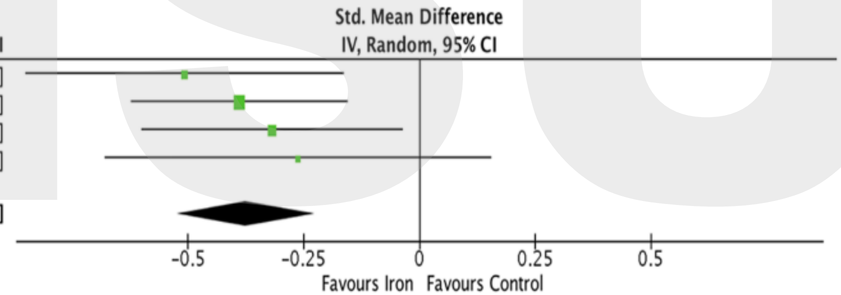
Low M, et al. CMAJ. 2013 (185): E791-E802.

Iron deficiency: non-heme treatment effects

Study or Subgroup	Iron Therapy Mean	Iron Therapy SD	Iron Therapy Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Verdon 2003	-1.82	1.7	71	-0.85	2.1	65	18.8%	-0.51 [-0.85, -0.17]
Favrat 2014	-2.2	2.1	144	-1.4	2	146	40.6%	-0.39 [-0.62, -0.16]
Vaucher 2012	-12.2	10.2	102	-8.7	11.7	96	27.9%	-0.32 [-0.60, -0.04]
Krayenbuehl 2011	-1.3	1.4	43	-0.9	1.6	47	12.7%	-0.26 [-0.68, 0.15]
Total (95% CI)			**360**			**354**	**100.0%**	**-0.38 [-0.52, -0.23]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.02$, df = 3 (P = 0.80); $I^2 = 0\%$

Test for overall effect: Z = 4.97 (P < 0.00001)



- Meta-analysis found that iron supplementation improves fatigue scores
- Fatigue is most likely to improve in patients with ferritin < 50 ng/mL

Iron deficiency: lack of response

- Symptoms persist – particularly fatigue, restless legs, pagophagia
- The hematological effects are the ones we see most readily, but are just the tip of the iron deficiency iceberg.

Iron deficiency: lack of response

Usually due to:

- Difficulty taking the iron – tastes terrible, GI side effects, just forget
- Difficulty changing diet
- Haven't fixed the bleeding problem

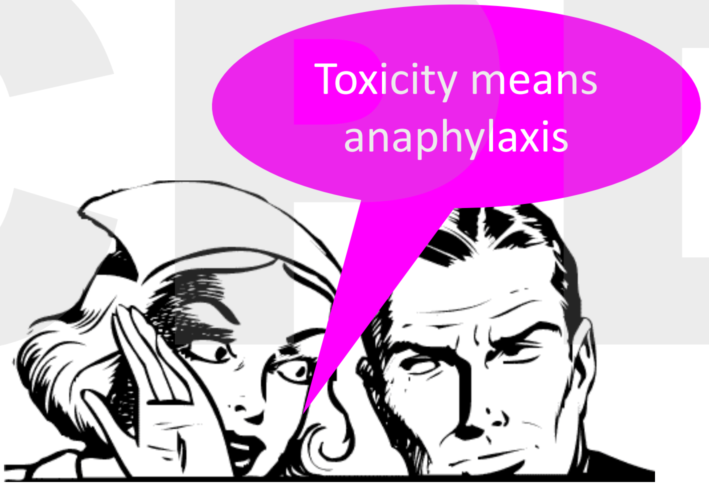
Iron deficiency: parenteral iron

Indications:

- Unable to tolerate or take oral iron
- Inability to absorb oral iron
- Difficulty in keeping up with losses

Iron deficiency: parenteral iron

- Remember: "Unbound iron has unbridled redox activity…" - Nancy Andrews, Christina Ulrich, and Mark Fleming
- Original iron preparations resulted in release of free iron which resulted in a lot of toxicity
- Sugars were introduced as chaperones but there was still a lot of toxicity



Iron deficiency: parenteral iron

	Sugar ligand	Relative stability	Relative labile iron release	Max single dose	Minimum admin time	Only one dose needed?	Likelihood of insurance approval

Iron deficiency: parental iron

Table 2. Severe adverse events reported with IV iron relative to any comparator (placebo, no iron, oral iron, intramuscular iron)

Severe adverse events	RR (95%)
All iron studies	1.04 (0.93-1.17)
SAE by compound	
Ferric carboxymaltose	0.82 (0.64-1.06)
Ferric gluconate	1.12 (0.96-1.30)
Ferumoxytol	1.04 (0.71-1.53)
Iron dextran	1.05 (0.77-1.45)
Iron isomaltose/polymaltose	1.09 (0.43-2.80)
Iron sucrose	1.33 (0.96-1.83)
Infusion reactions	2.47 (1.43-4.28)*
Mortality	1.06 (0.81-1.39)
Infections	1.17 (0.83-1.65)
Gastrointestinal	0.55 (0.51-0.61)*

No fatal reactions or anaphylaxis reported in 103 trials composing 10 390 treated with IV iron. Adapted from Avni et al[26] with permission.
*Significant.

- Previous reports of high rates of adverse events were likely related to HMWID
- Once HMWID was removed from analyses, the rate of adverse events went to < 1:200,000 doses
- Even minor reactions are uncommon ~1:200 doses

Auerbach M, et al. ASH Education Book. 2016.

Iron deficiency: parental iron

TABLE II. Baseline Characteristics of the Participating Subjects

Baseline laboratory parameters	Mean (SD)
Hemoglobin (anemic) (g dl^{-1})	11.3 (0.2)
Hemoglobin (nonanemic) (g dl^{-1})	12.9 (0.3)
Ferritin (ng ml^{-1})	13.4 (13.1)
Serum Iron (μg dl^{-1})	53.2 (27.8)
MCV (fL)	81.9 (6.3)
RDW (%)	14.5 (1.8)
Iron saturation (%)	14 (6.9)
TIBC (μg dl^{-1})	395.8 (59.8)
CHr (pg)	29 (3.98)
Symptoms of iron deficiency	Number of patients reported
Seep disturbances	14 (70%)
Difficulty concentrating	15 (75%)
Unexplained headaches	16 (80%)
Tension in the neck	13 (65%)
Restless legs	5 (25%)
Excessive hair loss	5 (25%)
Brittle nails and nail breakage	5 (25%)
Baseline co-morbid conditions	Number of patients reported
Obese/overweight	6 (30%) / 5 (25%)[a]
Heavy menstrual bleeding	15 (75%)
Platelet function defects	7 (35%)
Von Willebrand disease	1
Ehlers Danlos syndrome	1
Gastrointestinal illness	2[b]
Fibromyalgia	2

- Study of 21 adolescent women receiving IV iron
- Received 4 doses of iron sucrose over 2 weeks
- Fatigue scores with pedsQL surveys

Iron deficiency: parenteral iron

TABLE III. Least-Square Means (Standard Error) [Tukey-adjusted *P* values Compared to Screening Values] of Laboratory Parameters and Peds QL™ Multidimentional Fatigue Scale for Different Time Points

	Screening mean (SE)	4th infusion; mean (SE);[a](*P* value)	6 Weeks; mean (SE);[a] (*P* value)	3 Months; mean (SE);[a](*P* value)	6 Months; mean (SE);[a] (*P* value)
Ferritin (ng ml^{-1})	13.4 (20.3)	224.3 (20.3) ($P < 0.0001$)	139.7 (21.2); ($P < 0.0001$)	82.0 (21.6); ($P = 0.049$)	105.1 (27.0); ($P = 0.02$)
Peds QL patient	35.2 (4.3)	51.7 (4.4); ($P = 0.003$)	59.3 (4.6); ($P < 0.0001$)	63.3 (4.6); ($P < 0.0001$)	56.4 (5.4); ($P = 0.002$)
Peds QL parent	31.9 (5.3)	59.3 (5.4); ($P < 0.0001$)	57.8 (5.6); ($P < 0.0001$)	66.5 (5.5); ($P < 0.0001$)	60.5 (6.8); ($P = 0.0004$)
Hemoglobin (g dl^{-1}); anemic (Hb <12); $n = 12$	11.3 (0.2)	11.6 (0.2) [$P = 0.99$]	12.6 (0.3) [$P = 0.001$]	12.8 (0.2) [$P < 0.0001$]	12.7 (0.3) [$P = 0.008$]
Nonanemic (Hb>12) $n = 8$	12.9 (0.3)	12.7 (0.3) [$P = 0.99$]	13.4 (0.3) [$P = 0.85$]	13.7 (0.3) [$P = 0.46$]	13.8 (0.3); [$P = 0.3$]
Iron (μg ml^{-1})	53.2 (7.5)	85.4 (7.8) [$P = 0.004$]	81.4 (7.8) [$P = 0.017$]	87.9 (8.0) [$P = 0.002$]	93 (10.4) [$P = 0.006$]
CHr	28.9 (0.6)	31.9 (0.7) [$P = 0.001$]	31.9 (0.7) [$P = 0.0017$]	31.2 (0.8) [$P = 0.06$]	30.3 (1.4) [$P = 0.86$]

[a] *P* value compared to screening.

IV iron corrected iron deficiency and resulted in improved quality of life scores with no serious adverse events.

Sharma R, et al. American Journal of Hematology. 2016 (91): 973-977.

Iron deficiency: parenteral iron

My approach to IV Iron:

- Patient indicates that they cannot tolerate oral iron
- Patient indicates that they will not take oral iron
- Patient has been on oral iron for 3 months with no change in iron parameters
- Patient has severe anemia
- Patient has ongoing significant blood losses
- Patient and family understand risk of adverse events

My approach to IV iron:

- I give a lot of IV iron.

Iron deficiency

Iron deficiency: A few pearls

- If it's a little kid who drinks a lot of milk, start oral iron 3 mg/kg/day as a single dose and decrease milk intake
- If it's a teenage girl, start oral iron and if their periods are heavy, start something to control periods
- If it's a teenage boy, do more work up
- Remind them of the neurocognitive effects and that treating iron deficiency is important for the future of our world!
- If they don't get better, send them over so we can either:
  - ~~Scare them~~ Be a reassuring encouraging consultant that stresses the importance of iron on cognitive development
  - Figure out a different diagnosis
  - Give IV iron

Iron deficiency: in summary

- Iron deficiency is very common, especially in young children and adolescent young women
- Iron deficiency can result in a variety of symptoms or none at all
- Screening high risk populations regardless of symptoms is important
- Iron deficiency can have long lasting adverse effects on cognition
- Treatment of iron deficiency can be difficult
- IV iron isn’t as scary as it used to be

Thank You