Iron Deficiency Anemia

Kristina Haley, DO, MCR

Associate Professor

Pediatric Hematology/Oncology

Disclosures

- I have no relevant financial disclosures
- I do receive funding to study women & girls with bleeding disorders from the American Thrombosis & Hemostasis Network and the Hemostasis & Thrombosis Research Society

Objectives

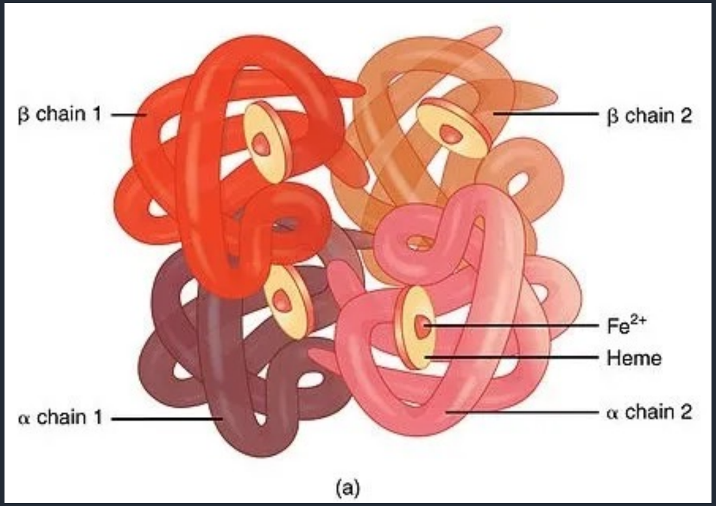
1. Identify causes of anemia
2. Explain iron economy.
3. List risk factors for the development of iron deficiency.
4. Describe the consequences of iron deficiency.

Blood!

- Red Blood Cells- biconcave discs filled with hemoglobin with the job of transporting oxygen and carbon dioxide

Hemoglobin

- Hemoglobin is the protein in red blood cells that carries oxygen and carbon dioxide
- Each red cell can contain 300 million hemoglobin molecules!
- Each hemoglobin contains 4 subunits (globins) and 4 heme groups
  - The heme groups contain iron, which binds the oxygen



https://www.differencebetween.com/difference-between-oxygenated-and-vs-deoxygenated-hemoglobin/

red blood cell indices

MCV, MCHC, MCH, RBC, RDW: who cares?!

MCV: how big are the red cells on average

MCHC: what is the concentration of hemoglobin inside each red cell

MCH: i don't use this one!

RBC: how many red cells are there? are there a bunch of tiny cells? Or not a lot of tiny cells?

RDW: is the population of red cells heterogeneous?

Normal values for infants & children

APPENDIX 9 Normal Hematologic Values During the First Year of Life in Healthy Term Infants*

	AGE (mo)						
n	0.5 (n = 232)	1 (n = 240)	2 (n = 241)	4 (n = 52)	6 (n = 52)	9 (n = 56)	12 (n = 56)
Hemoglobin (mean ± SE)	16.6 ± 0.11	13.9 ± 0.10	11.2 ± 0.06	12.2 ± 0.14	12.6 ± 0.10	12.7 ± 0.09	12.7 ± 0.09
−2 SD	13.4	10.7	9.4	10.3	11.1	11.4	11.3
Hematocrit (mean ± SE)	53 ± 0.4	44 ± 0.3	35 ± 0.2	38 ± 0.4	36 ± 0.3	36 ± 0.3	37 ± 0.3
−2 SD	41	33	28	32	31	32	33
RBC count (mean ± SE)	4.9 ± 0.03	4.3 ± 0.03	3.7 ± 0.02	4.3 ± 0.06	4.7 ± 0.05	4.7 ± 0.04	4.7 ± 0.04
−2 SD +2 SD	3.9-5.9	3.3-5.3	3.1-4.3	3.5-5.1	3.9-5.5	4.0-5.3	4.1-5.3
MCH (mean ± SE)	33.6 ± 0.1	32.5 ± 0.1	30.4 ± 0.1	28.6 ± 0.2	26.8 ± 0.2	27.3 ± 0.2	26.8 ± 0.2
−2 SD	30	29	27	25	24	25	24
MCV (mean ± SE)	105.3 ± 0.6	101.3 ± 0.3	94.8 ± 0.3	86.7 ± 0.8	76.3 ± 0.6	77.7 ± 0.5	77.7 ± 0.5
−2 SD	88	91	84	76	68	70	71
MCHC (mean ± SE)	314 ± 1.1	318 ± 1.2	318 ± 1.1	327 ± 2.7	350 ± 1.7	349 ± 1.6	343 ± 1.5
−2 SD	281	281	283	288	327	324	321

Nathan & Oski's, 7th edition.

Normal values for infants & children

APPENDIX 11 Normal Hematologic Values in Children*

Age	HEMOGLOBIN (g/dL)		HEMATOCRIT (%)		RED CELL COUNT (10^{12}/L)		MCV (fL)		MCH (pg)		MCHC (g/dL)	
	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD
Birth (cord blood)	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30
1 to 3 days (capillary)	18.5	14.5	56	45	5.3	4.0	108	95	34	31	33	29
1 week	17.5	13.5	54	42	5.1	3.9	107	88	34	28	33	28
2 weeks	16.5	12.5	51	39	4.9	3.6	105	86	34	28	33	28
1 month	14.0	10.0	43	31	4.2	3.0	104	85	34	28	33	29
2 months	11.5	9.0	35	28	3.8	2.7	96	77	30	26	33	29
3 to 6 months	11.5	9.5	35	29	3.8	3.1	91	74	30	25	33	30
0.5 to 2 years	12.0	10.5	36	33	4.5	3.7	78	70	27	23	33	30
2 to 6 years	12.5	11.5	37	34	4.6	3.9	81	75	27	24	34	31
6 to 12 years	13.5	11.5	40	35	4.6	4.0	86	77	29	25	34	31
12 to 18 years												
Female	14.0	12.0	41	36	4.6	4.1	90	78	30	25	34	31
Male	14.5	13.0	43	37	4.9	4.5	88	78	30	25	34	31
18 to 49 years												
Female	14.0	12.0	41	36	4.6	4.0	90	80	30	26	34	31
Male	15.5	13.5	47	41	5.2	4.5	90	80	30	26	34	31

Nathan & Oski's, 7th edition.

Anemia = low hemoglobin

Buchanan's Rules:

- 11 + [0.1 x (age in years)] = lower limit of normal for hemoglobin

- 70 + [1 x (age in years)] = lower limit of normal for MCV

Anemia - testing

- Point of care hemoglobin
  - Advantages: in the office, immediate results, ”just” a finger poke
  - Disadvantages: do not get any other info about the red cells
- Venipuncture CBC
  - Advantages: get all the red cell scoop
  - Disadvantages: requires a venous puncture, not immediate

Anemia - causes

Is the hemoglobin normal for age?

yes → Good job! You cured them!

MCV

microcytic

- Iron deficiency
- Hemoglobinopathy
- Lead poisoning
- Sideroblastic anemia
- Anemia of chronic disease

normocytic

- Viral suppression
- Acute blood loss
- Renal disease
- Anemia of chronic disease
- Hemolysis
- Marrow infiltration
- Dyserythropoietic anemia
- Liver disease

macrocytic

- B12 deficiency
- Folate deficiency
- Hemolysis
- hypothyroidism
- Down Syndrome
- Myelodysplasia
- Marrow infiltration
- Marrow failure
- Medications
- Liver disease

Anemia - causes

Is the hemoglobin normal for age?

no

yes → Good job! You cured them!

Destruction

- Hemoglobinopathy
- Enzymopathy
- Membranopathy
- Autoimmune
- hypersplenism

Production

- Aplastic anemia
- Viral suppression
- Marrow infiltration
- Marrow failure
- Iron deficiency anemia
- Other nutritional deficiency

Loss

- GI loss
- GU loss
- Menstrual losses
- Trauma
- Blood draws

Anemia - causes

- While there are many causes of anemia in children, the most common cause is iron deficiency.
- It is important to recognize, though, that iron deficiency can occur without anemia

Iron

"Iron lacks the glitter of gold and the sparkle of silver but outshines both in biologic importance."

- Nancy Andrews, Christina Ulrich, and Mark Fleming

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

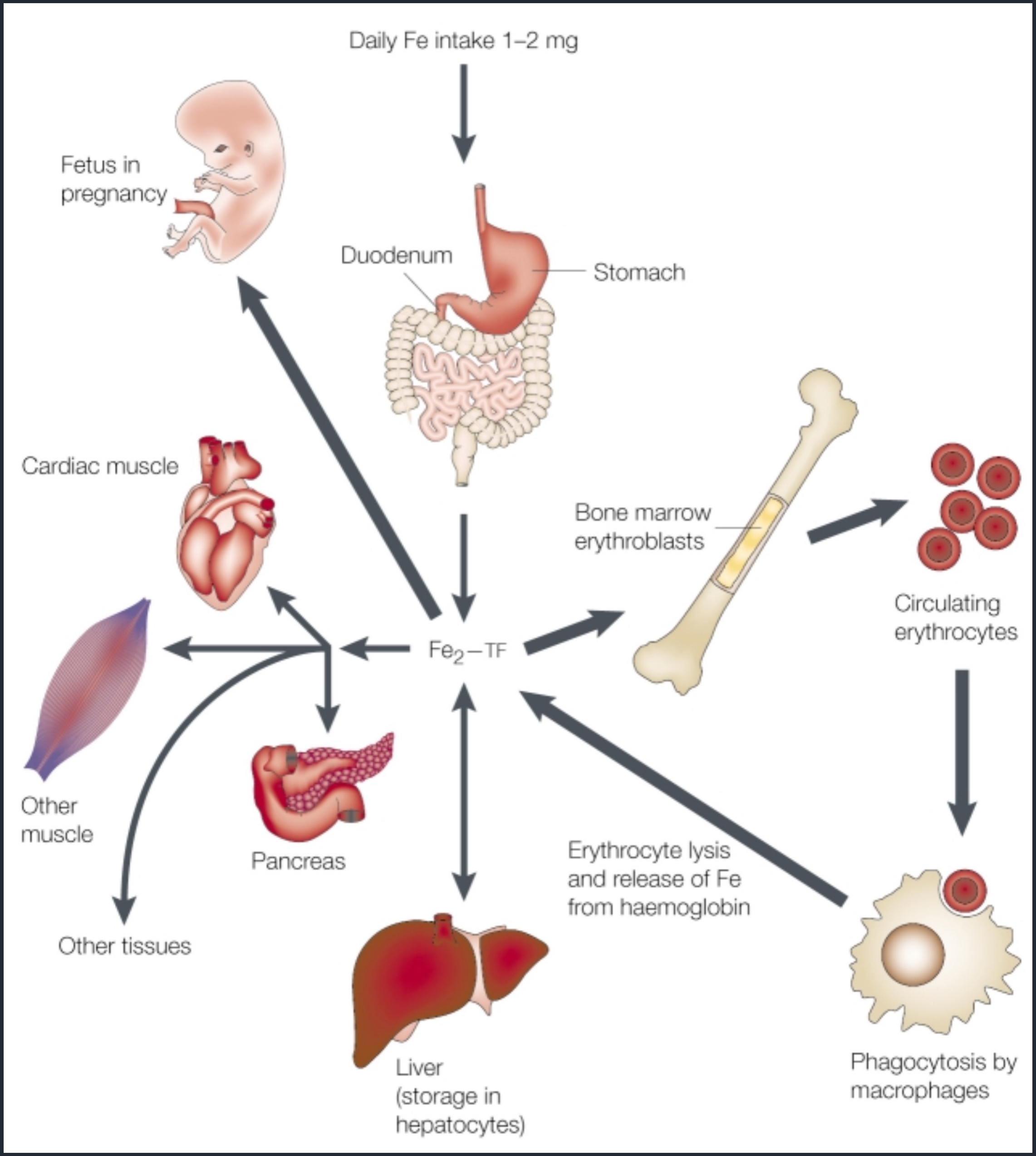
Iron-pretty important.

"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 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



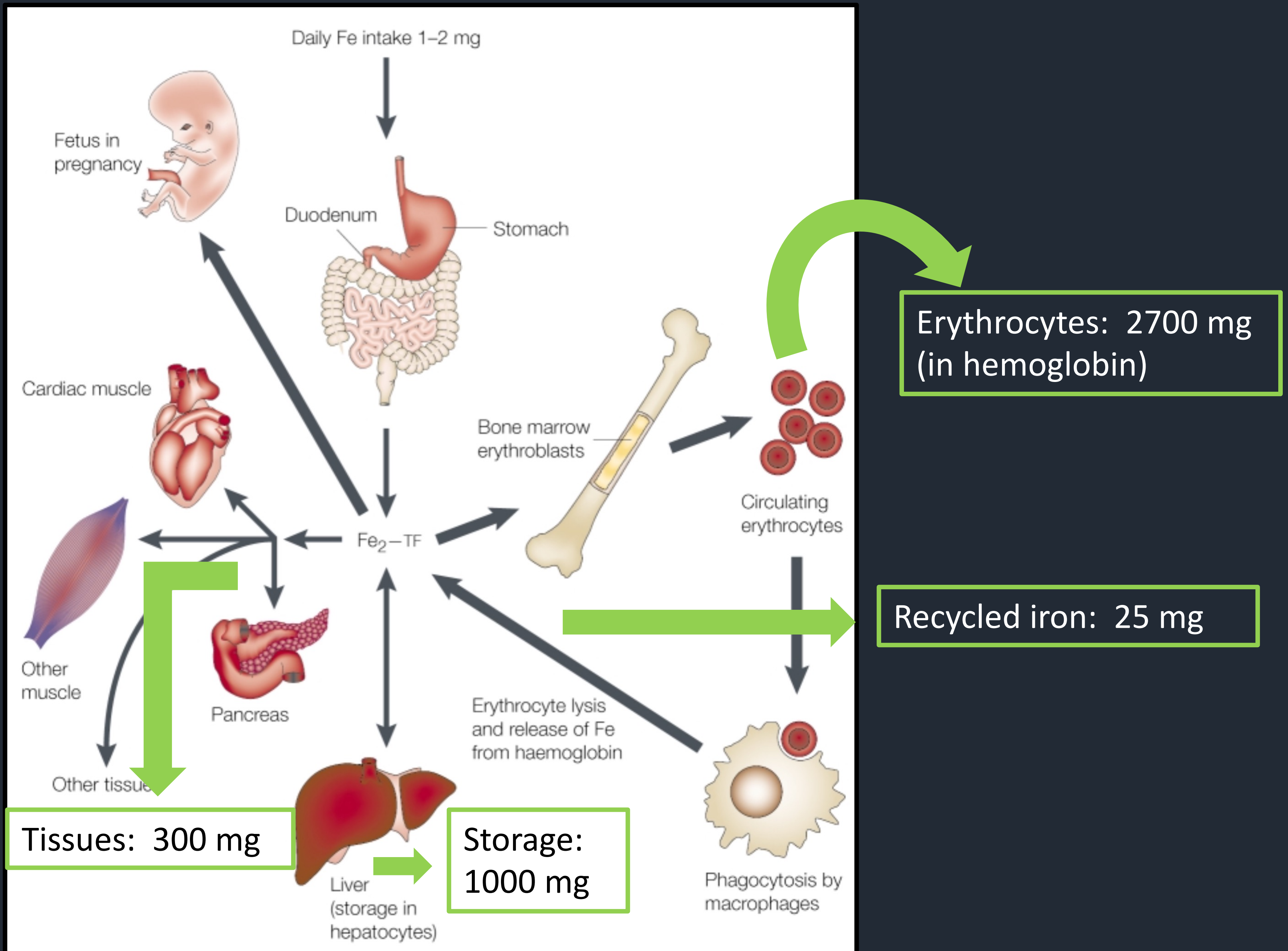
Iron Economy:
The average adult has 4-5 g of body iron.

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

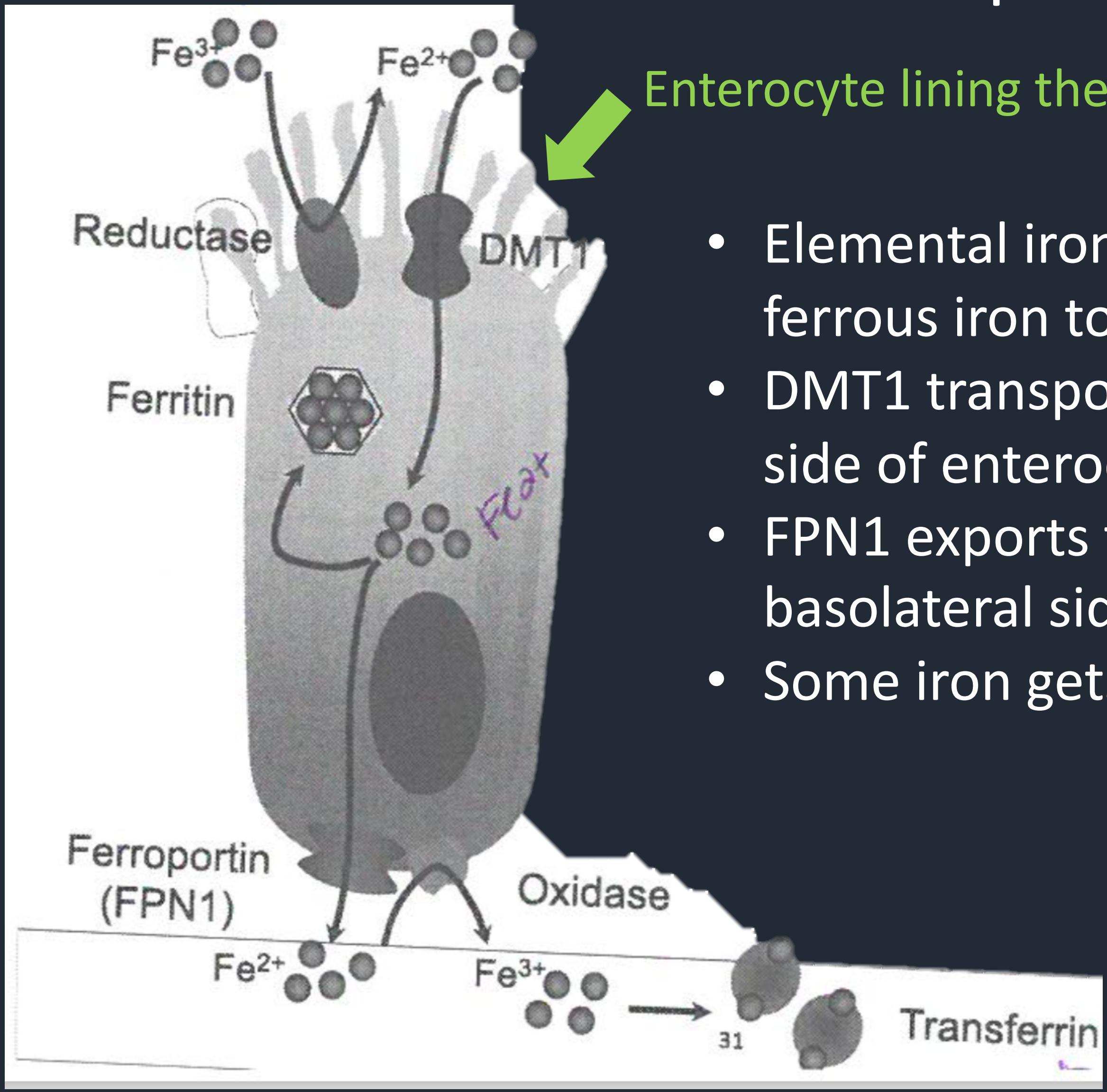


Adapted from Andrews NC Nat Rev Gen 2000 (1): 208-217 and Nutritional Anemias by Matthew Heeney, ASPHO review course

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

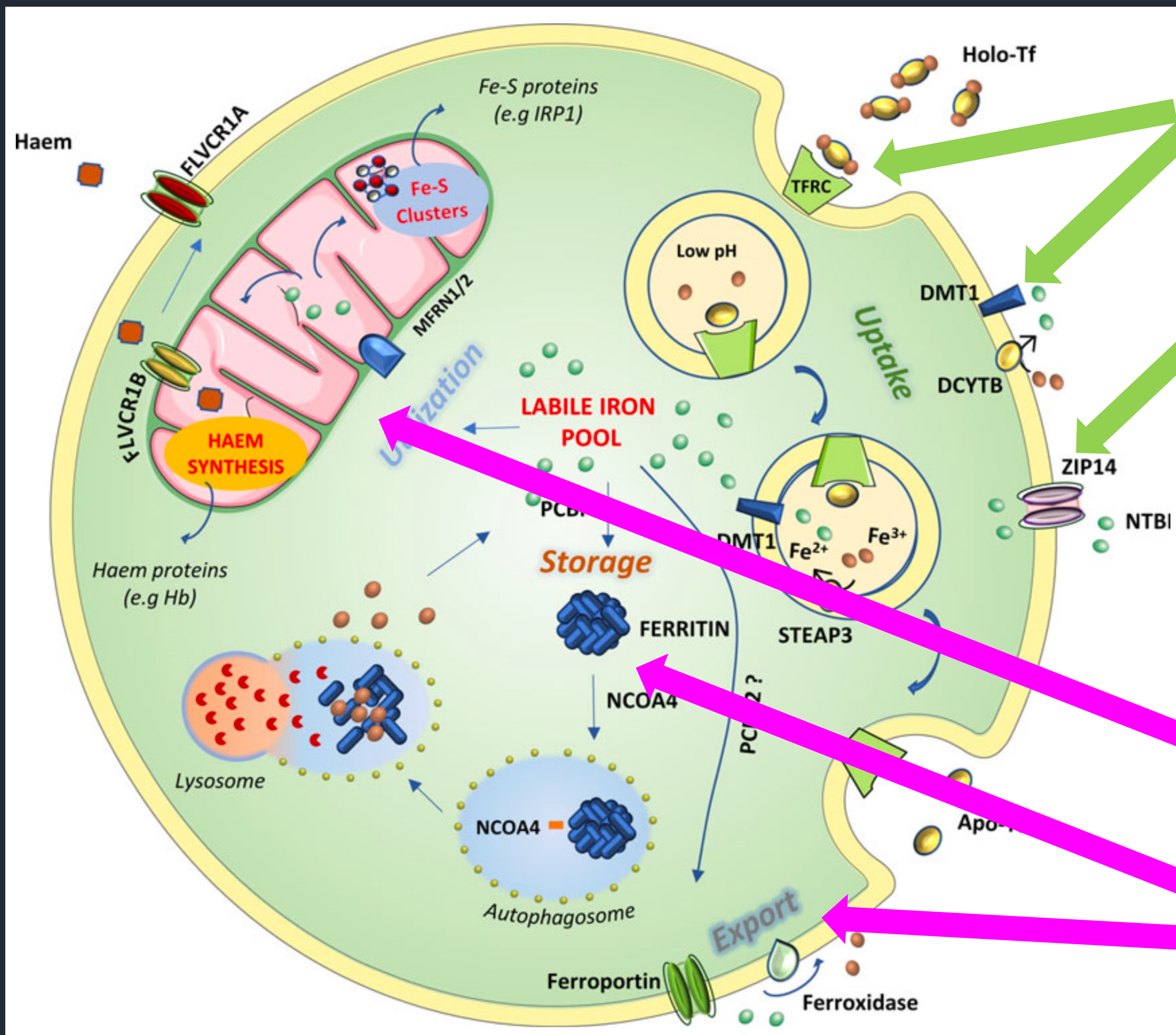
Intestinal iron absorption

- Heme iron: the iron found in meat, poultry, and fish (blood and muscle)
- Non-heme iron: plant foods like 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 milk
	Antacids

Iron trafficking



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

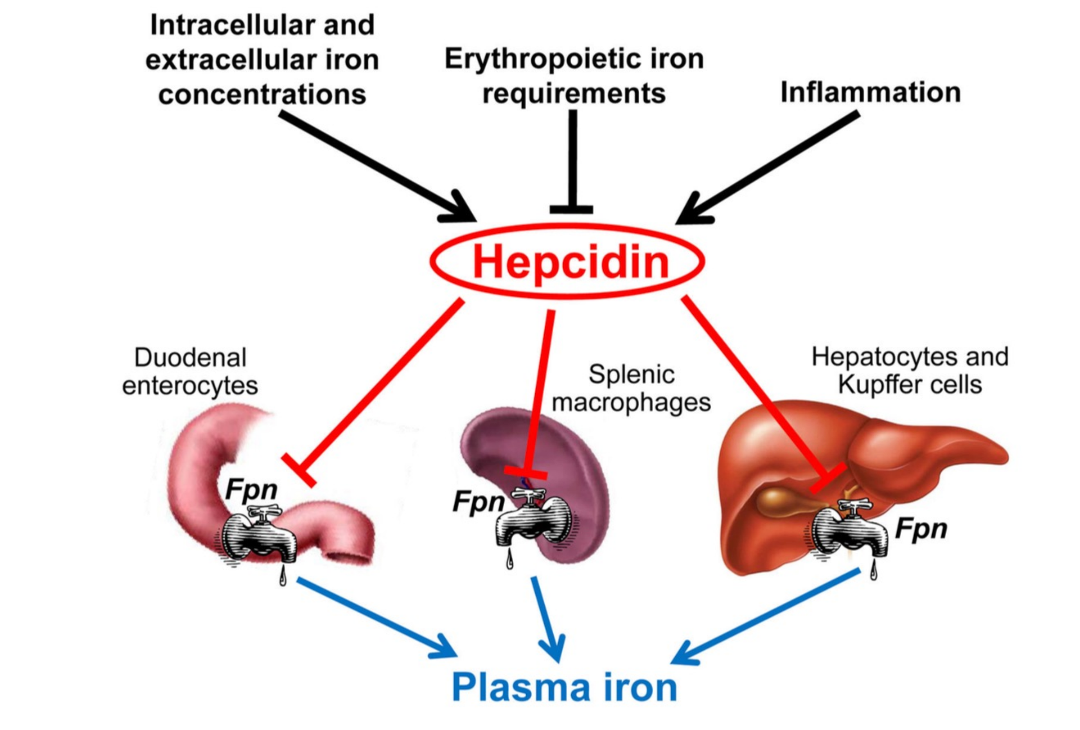
Zinc transporter protein (ZIP14) takes up iron in iron overload states

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.

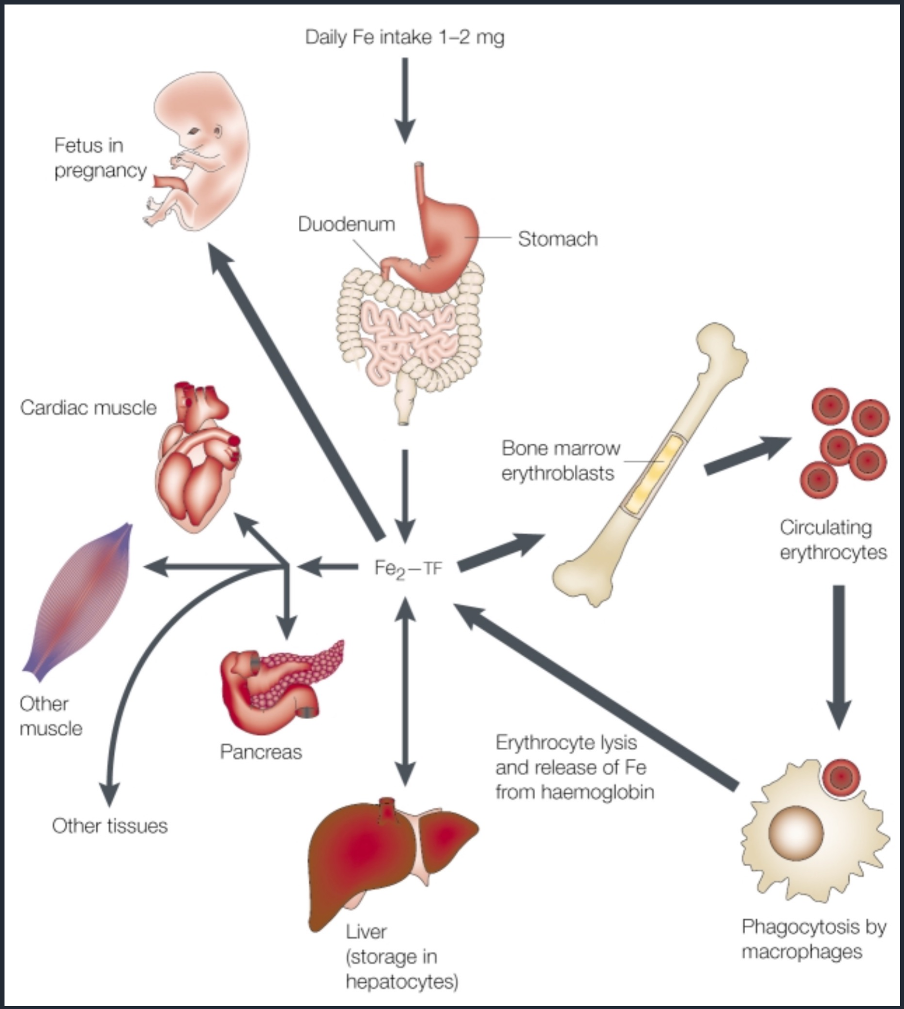
Systemic iron regulation: Hepcidin



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

Table 3.—Prevalence of Iron Deficiency and Iron Deficiency Anemia, All Races, NHANES III 1988-1994*

Sex and Age, y	No.	Iron Deficiency, %	Iron Deficiency Anemia, %
Both sexes			
1-2	1339	9	3†
3-5	2334	3	<1
6-11	2813	2	<1
Females			
12-15	786	9	2†
16-19	700	11†	3†
20-49	4495	11	5†
50-69	2034	5	2
≥70	1630	7†	2†
Males			
12-15	691	1	<1
16-19	658	<1	<1
20-49	4048	<1	<1
50-69	1929	2	1
≥70	1437	4	2

*NHANES indicates National Health and Nutrition Examination Survey.

†Prevalence in nonblacks is 1% lower than prevalence

Non-pregnant women of reproductive age

24,894 persons aged 1 year and older included in this cross-sectional survey from 1988-1994

Prevalences correspond to

-700,000 toddlers with iron deficiency, with 240,000 being anemic

-7.8 million women with iron deficiency, with 3.3 million being anemic

WHO global database on Anaemia – 1993-2005

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

Iron deficiency: epidemiology

- Updated NHANES data from 2007-2010

	n	Iron Deficiency [1]		Anemia [2]		Iron Deficiency Anemia [3]	
		%	95% Confidence Interval	%	95% Confidence Interval	%	95% Confidence Interval
1–5 years (12–71.9 months)	1437	7.1	(5.5, 8.7)	3.2	(2.0, 4.3)	1.1	(0.6, 1.7)
1–2 years (12–35.9 months)	643	13.5 *	(9.8, 17.2)	5.4 *	(3.5, 7.4)	2.7	(1.2, 4.2)
3–5 years (36–71.9 months)	794	3.7	(1.9, 5.5)	1.9	(0.7, 3.1)	- **	-

Extrapolating this data – 1.5 million children ages 1-5 years are at risk for iron deficiency.

Gupta PM, et al. Nutrients. 2016.

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.

Lopez, et al. The Lancet 2016 (387): 907-916.
Moore DF, et al. American Journal of Medicine 1994(97): 390-393.

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
- For infants – mom was iron deficient during pregnancy and breastfeeding

Iron deficiency: etiology

Too much out:

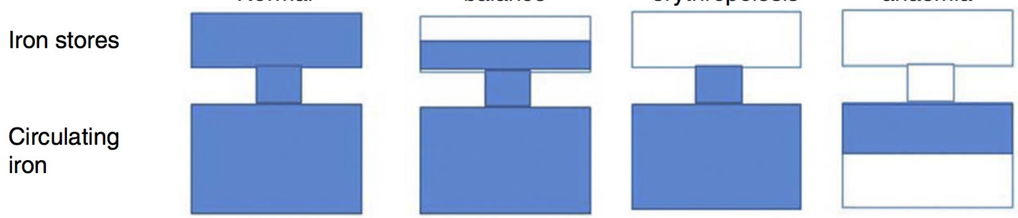
- GI blood loss (gastritis, ulcers, parasites, varices, IBD, etc)
- Recurrent prolonged epistaxis (check for bleeding disorders)
- Heavy menstrual bleeding (check for bleeding disorders)
- Hematuria (chronic infections)
- Pulmonary losses (pulmonary hemosiderosis)

Iron deficiency: etiology

Inadequate absorption:

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

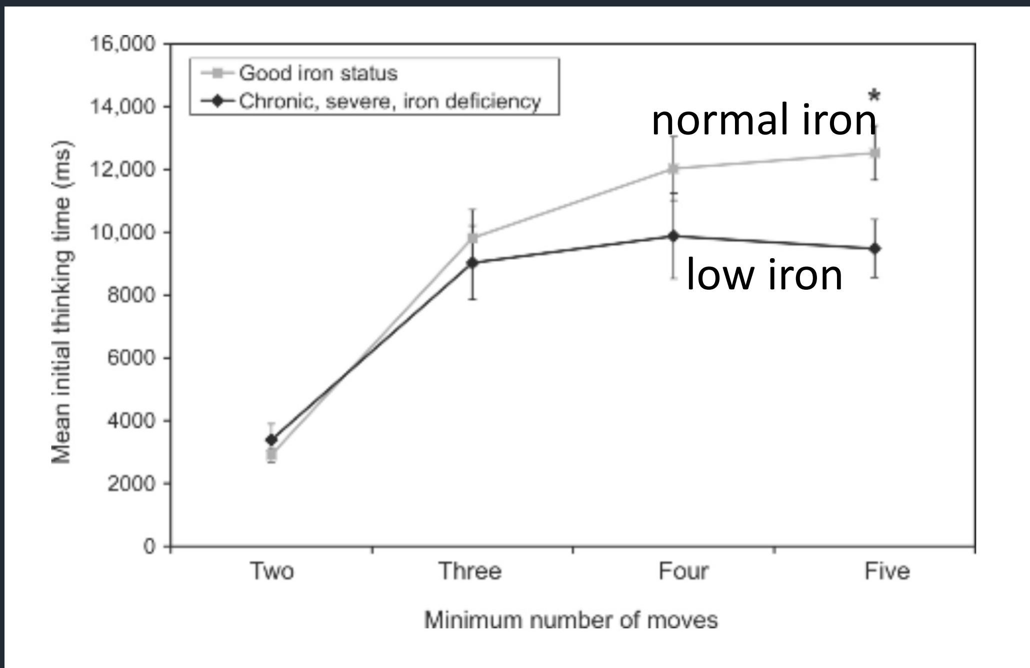
Iron deficiency: labs



	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

Iron deficiency

Iron deficiency: non-heme effects → neuro-cognitive

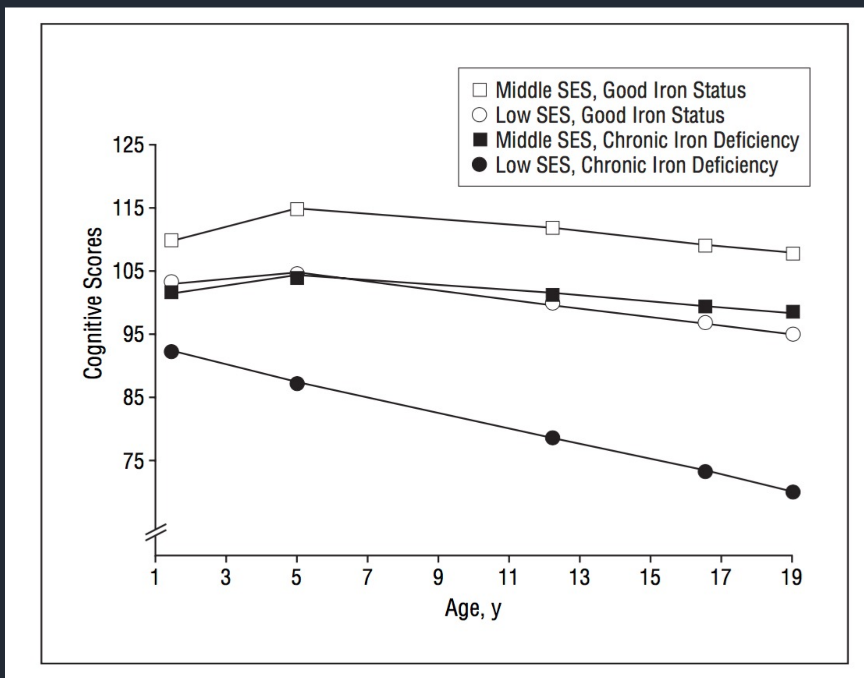


Adolescents who had been iron deficient as infants had difficulty forming and executing actions. They spent less time planning their response to the most challenging problems.

- Infants with iron deficiency anemia exhibit later 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

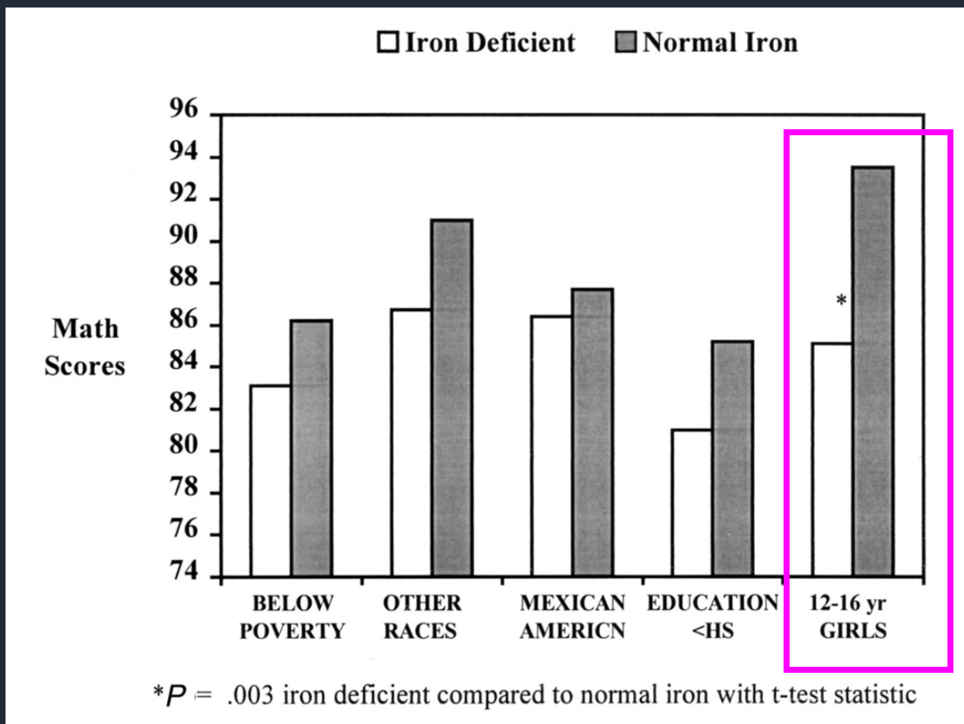


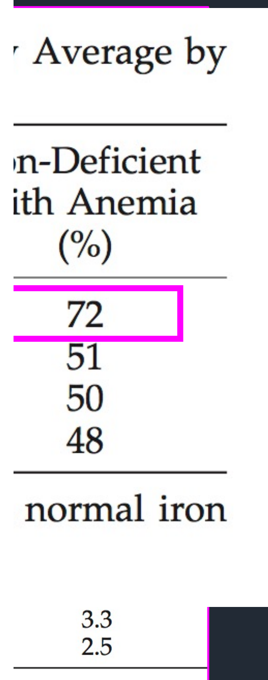
There is no evidence of catch-up in cognitive performance for individuals with chronic iron deficiency in infancy. And, there is a widening gap for those in low-SES families.

- 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, iron deficiency is associated with lower Health Related Quality of Life scores
- Fatigue is associated with lower ferritin levels
- 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: 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

Iron deficiency: treatment

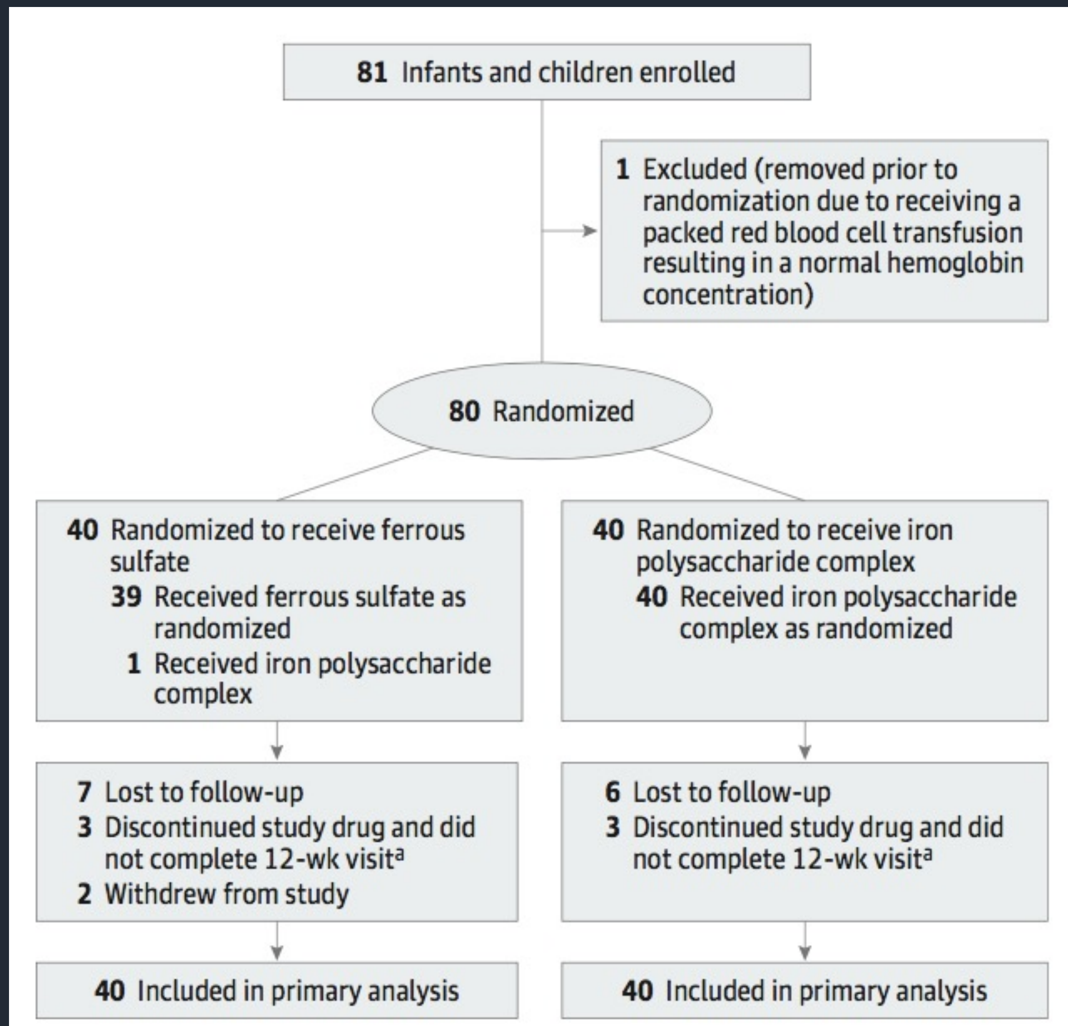
1) Correct the cause – stop bleeding, decrease milk intoxication, etc
2) Oral iron supplementation
3) IV iron supplementation

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

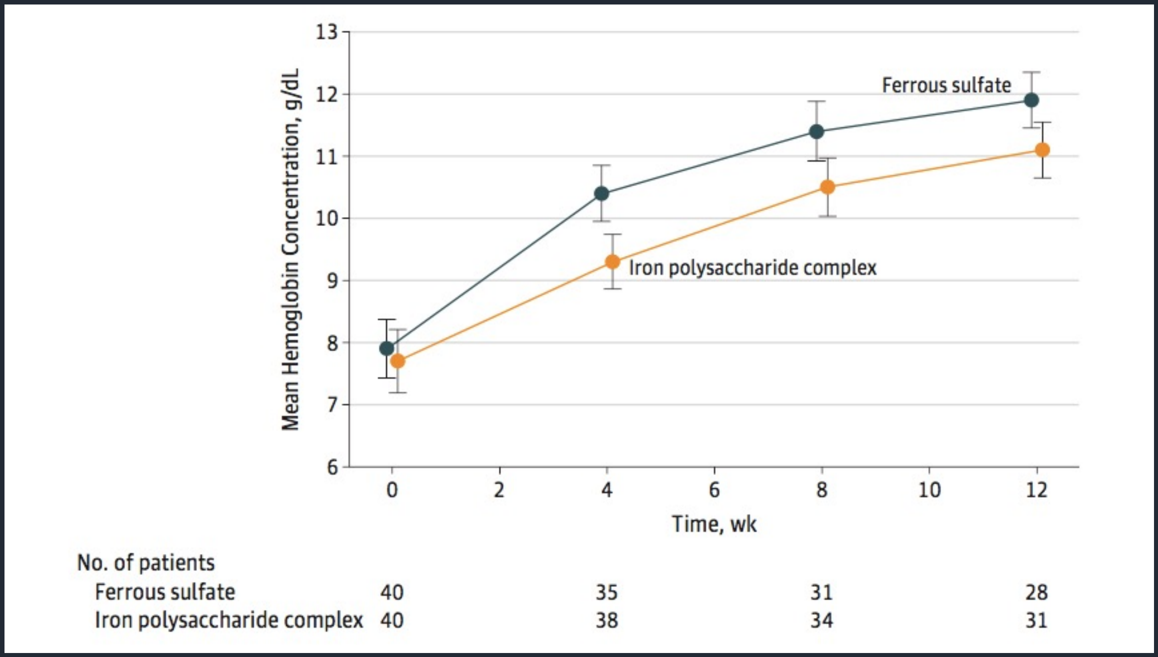
Iron deficiency: oral iron

Ferrous
Sulfate
3 mg/kg day
in single
dose



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

Iron deficiency: oral iron

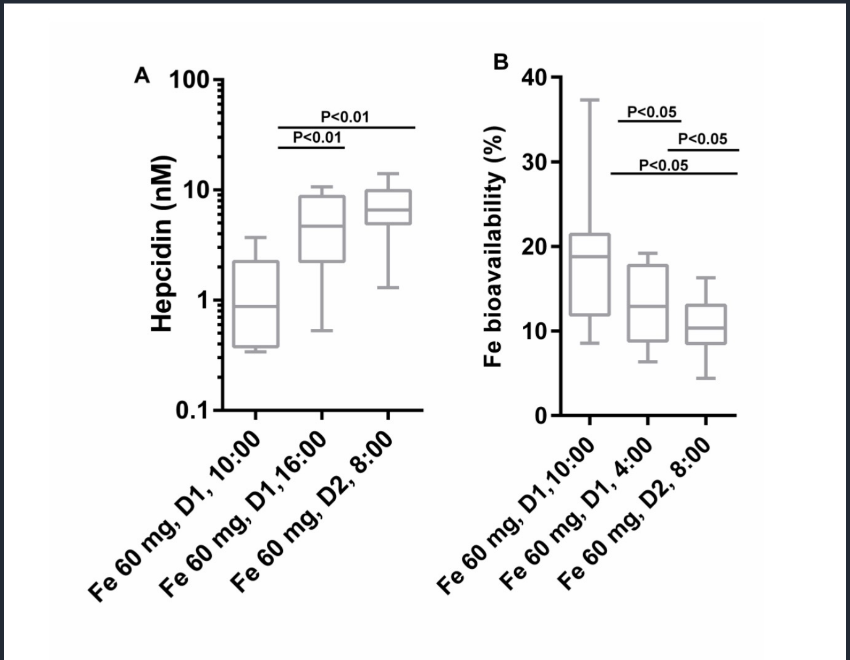


- Mean age of cohort= 23 months
- Complete resolution of iron deficiency anemia occurred in 29% of ferrous sulfate and 8% of iron polysaccharide
- Equivalent side effects in the two groups

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. (similar effect with daily 60 mg elemental iron.)

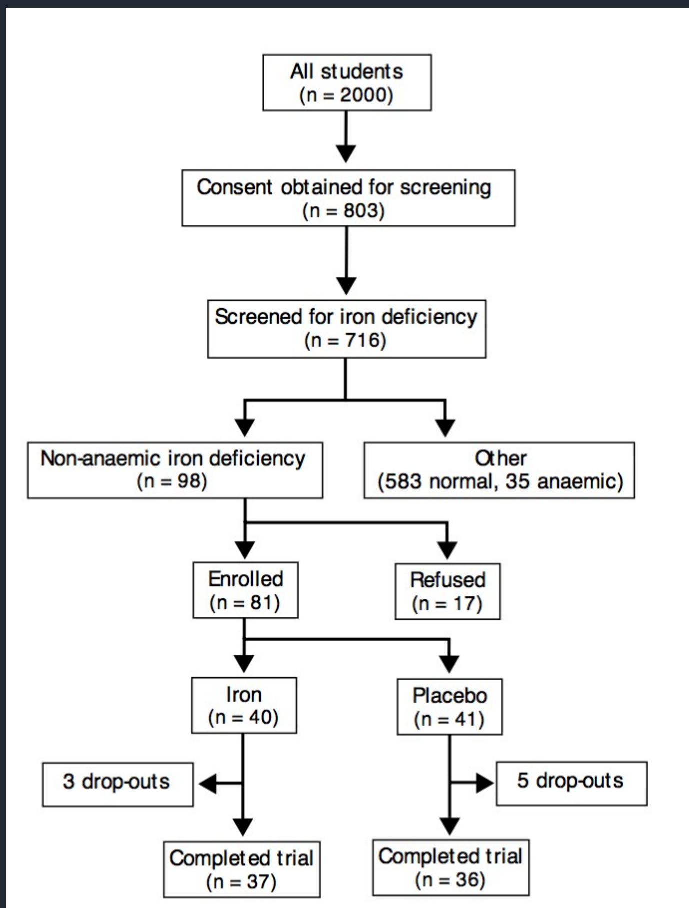
Iron deficiency: oral iron

- Iron deficient:
  - In infants and children: 3-6 mg/kg/day in a single dose
  - In adolescents and young adults: 65 mg elemental iron every other day or lower dose daily.
- Iron deficiency anemia:
  - In infants and children: up to 6 mg/kg/day in a single dose
  - In adolescents and young children: up to 120 mg/day in a single dose
- 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 whatever preparation results in the patient taking their iron

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
- Consider decreasing to 3 mg/kg/day (young kids) or 65 mg/day elemental (adolescents) after 4-6 weeks of supplementation to decrease side effects
- 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

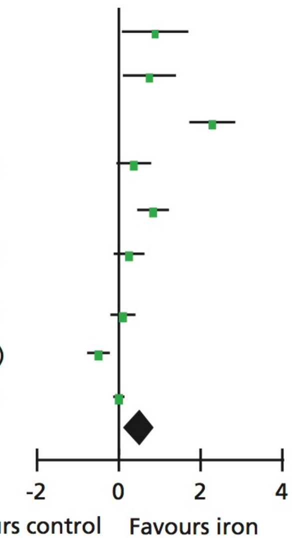
Iron supplementation in non-anemic adolescent women improved verbal learning scores but did not affect scores on attention tests.

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

Iron deficiency: non-heme treatment effects

Study	Test	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	SMD (95% CI)*
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)

SMD (95% CI)*



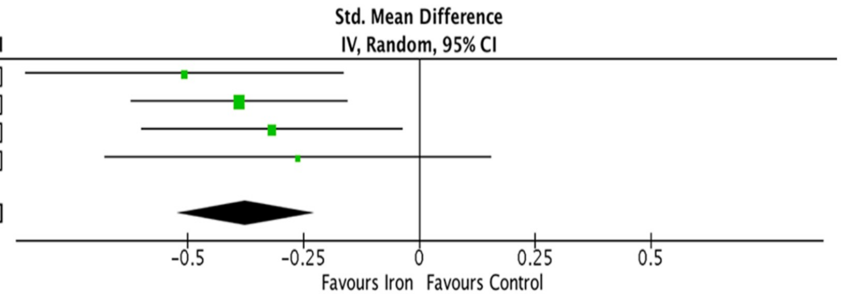
Meta-analysis found that iron supplementation in children ages 5-12 improved global cognitive scores, IQ (in anemic children), and measures of attention. Iron also improved height in iron deficient children and weight in anemic children. Iron supplementation reduced anemia risk by 50%.

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

Iron deficiency: non-heme treatment effects

	Iron Therapy			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	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

Houston BL, et al. BMJ Open. 2018 (8)

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

- 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
- Newer formulations are much better tolerated

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
Venofer	Sucrose	Medium	High	200 mg	30 min	NOPE	HIGH
Injectafer	Carboxy maltose	High	Low	1000 mg	15 min	YES	LOW
Infed	Dextran	High	Medium	20 mg/kg	60 min	YES	LOW
FeraHeme	Mannitol	High	Low	510 mg	15 min	Not usually	LOW

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: in summary

- Iron deficiency is very common, especially in young children and adolescent 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

Questions/Thoughts

”Anemia”