Iron Deficiency: Review

Melinda Wu, MD, MCR

Oregon Health & Science University

10/17/2019

Disclosure Information:

a) Moderators/panelists/presenters: Melinda Wu has nothing to disclose.
b) Funding sources: NIH/NHLBI- K08 HL133493

Objectives

1) To review iron body homeostasis
2) To review the etiologies of iron deficiency
3) To review various treatment options of iron deficiency

Part I:
Review of Iron Body Homeostasis

Iron Balance in the Body

Iron is required for growth of all cells, not just hemoglobin!

Heme proteins: cytochromes, catalase, peroxidase, cytochrome oxidase

Flavoproteins: cytochrome C reductase, succinic dehydrogenase, NADH oxidase, xanthine oxidase

Too little

Not enough for essential proteins:

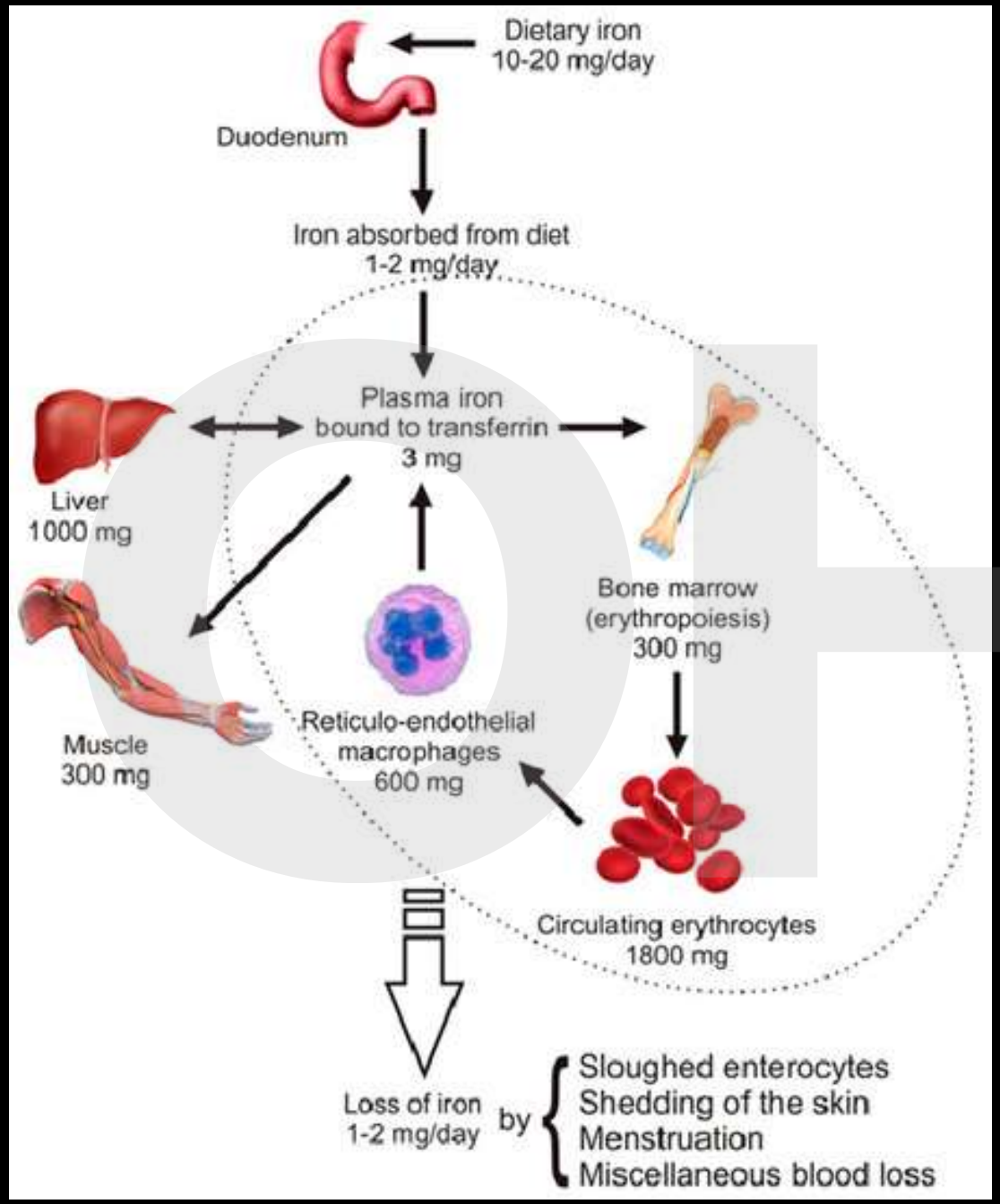
- Hemoglobin
- Ribonucleotide reductase (DNA synthesis)
- Cytochromes
- Oxidases

Too much

Accumulates in organs

Promotes the formation of:

- Oxygen radicals
- Lipid peroxidation
- DNA damage
- Tissue fibrosis

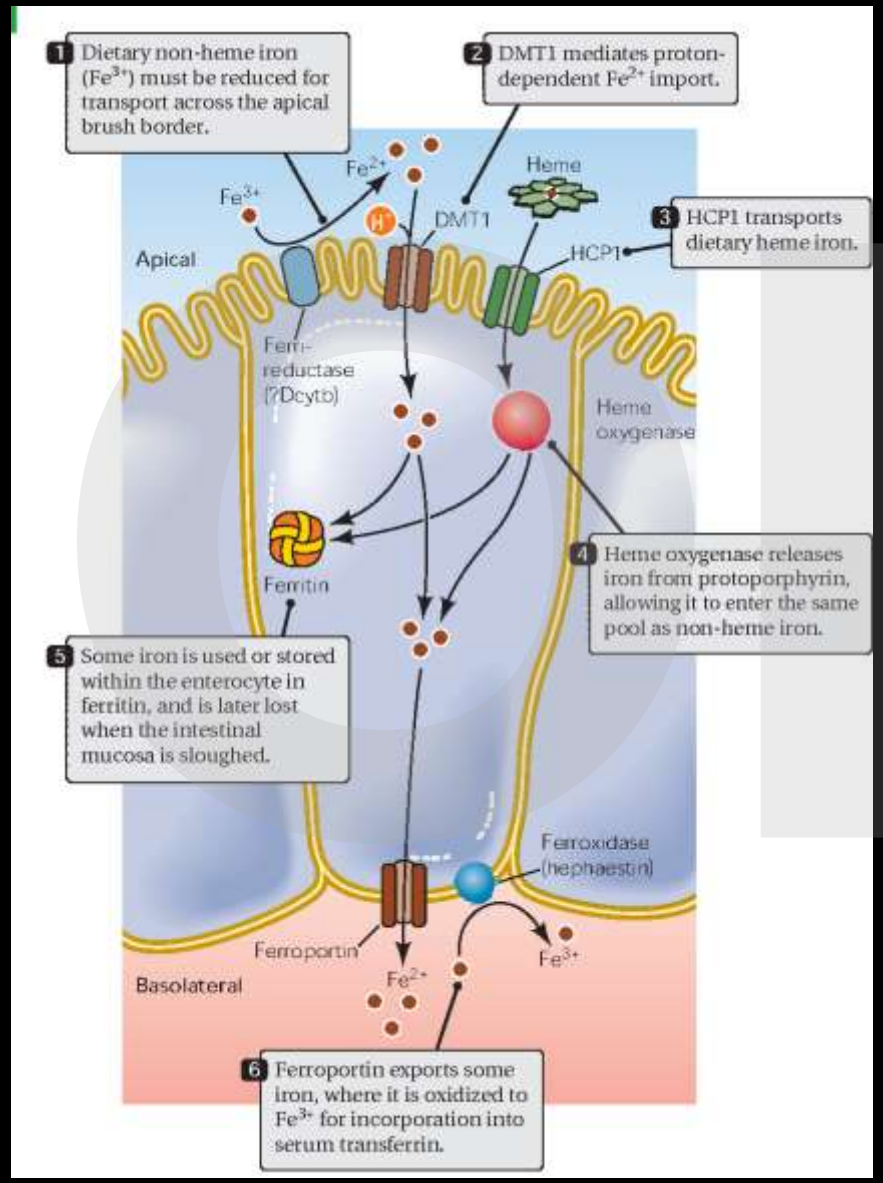


Lesjak, M.; K. S. Srai, S. Role of Dietary Flavonoids in Iron Homeostasis. *Pharmaceuticals* **2019**

Iron Economy

- The average adult has 4-5 g of body iron.
- ~10% of dietary iron absorbed, exclusively in duodenum
  - Varies with:
    - Iron content of diet
    - Bioavailability of dietary iron
    - Iron stores in body
    - Erythropoietic demand
    - Hypoxia
    - Inflammation
- More than half is incorporated into erythroid precursors/mature erythrocytes
- Only ~1-2 mg of iron enters and leaves the body in a day on average.
  - About 1 mg of iron is lost daily in menstruating women.

Systemic Iron Regulation: Absorption



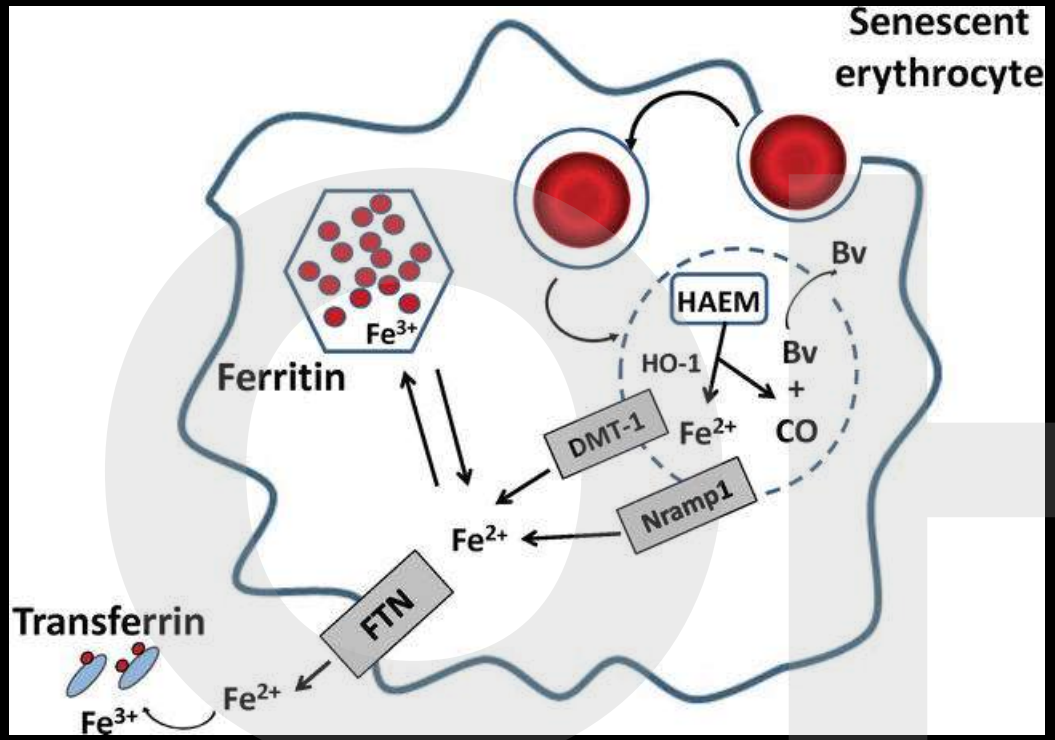
Donovan, Adriana et al. Physiology, 2006

<u>Iron status is regulated entirely at the level of absorption!</u>

- Heme iron (30-70%) > non-heme iron (<5%)
- 2 stable oxidation states: Ferrous (Fe 2+) > Ferric (Fe 3+)

- Elemental iron must be reduced to Fe2+ iron to be absorbed
  1. Feri-reductase converts Fe3+ to Fe2+
  2. DMT1 and HCP1 transport iron at the apical side of enterocytes
  3. Some iron gets complexed and stored as <u>ferritin</u>
  4. FPN1 exports Fe2+ at the basolateral side to then bind to <u>transferrin (Tf)</u>

Systemic Iron Regulation: Macrophage Recycling



Vaquero MP et al, intechopen, 2017.

Recycling is the major source of iron available for erythropoiesis!

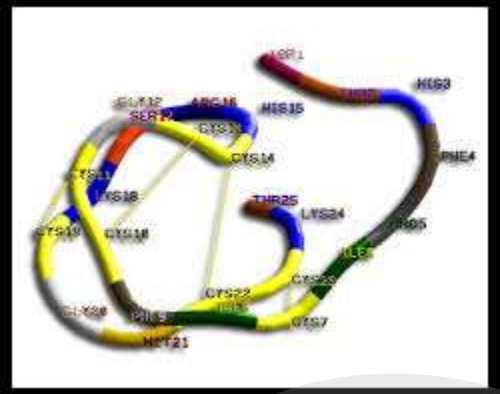
1. Macrophages engulf old or damaged RBCs and release heme from hemoglobin
2. Heme oxygenase releases iron from heme and begins the heme catabolic process
3. Iron recovered from heme may be:
   - Stored as ferritin
   - Exported to the plasma by Ferroportin where it is oxidized, binds Tf, and is available for erythropoiesis

Systemic Iron Regulation: Losses

- “Insensible” loss
- Physiological exfoliation: intestinal, skin cells
- Bleeding
- Reproductive

Iron loss is NOT regulated

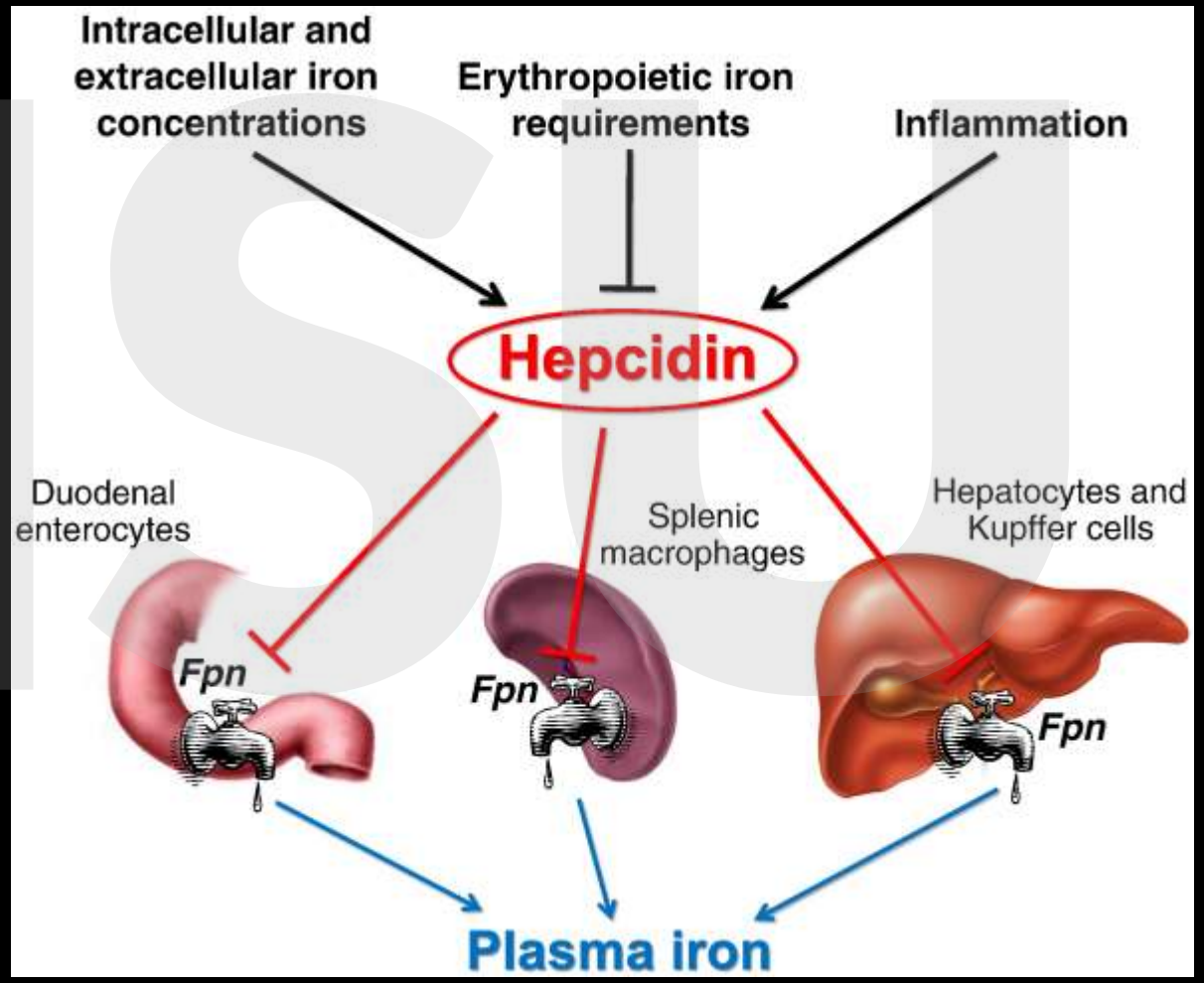
us.braun.com



Hepcidin: the iron regulatory hormone

- Hepcidin is a negative regulator of cellular iron export
  - Inhibits intestinal iron absorption
  - Inhibits macrophage iron release

Stimulus	*Hepcidin Response*
Iron deficiency	↓
Iron overload	↑↑
Increased erythroid demand	↓
Hypoxia	↓
Inflammation	↑



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

Part II:
Etiologies of iron deficiency

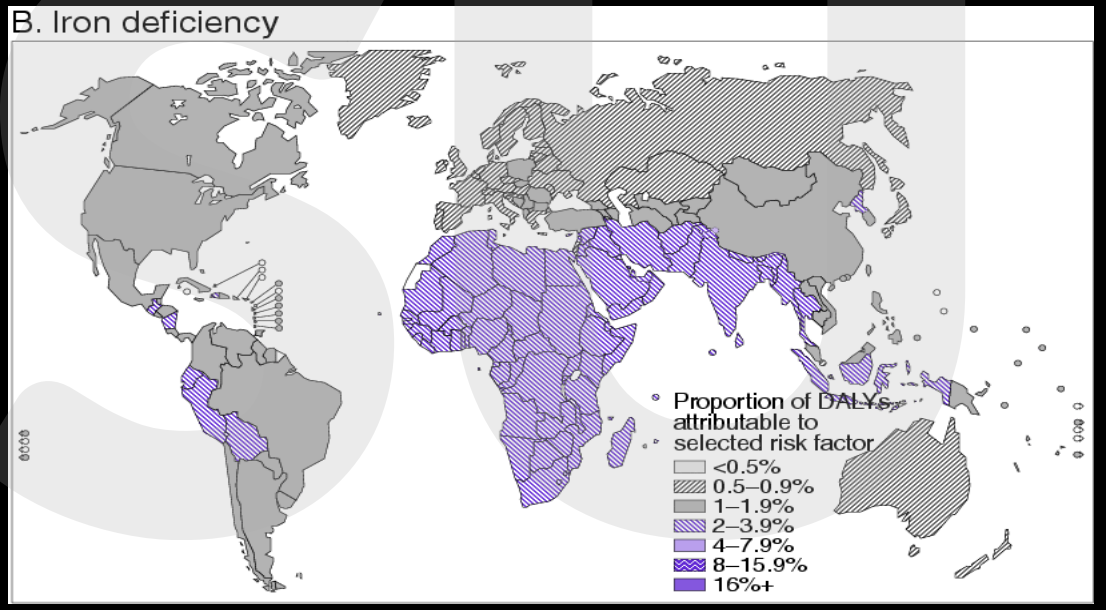
Iron Deficiency: Epidemiology

Globally: >1 billion people affected

- Multiple causes:
  - limited meat intake, vegetarian diet
  - GI bleeding/parasites (hookworms, schistosomiasis)
  - Limited availability of oral iron supplements

Confounders:

- Malaria
- Hemoglobinopathies (SCD, thalassemia)
- Inflammation
- Other nutritional deficiencies



www.who.int/whr/2002/

Iron Deficiency: Epidemiology

United States:

- Low income infants/toddlers
  - ~15% prevalence of iron deficiency (3% with IDA)
  - Increase in 1940's in part from recommendations to switch from breast feeding to cow milk-based formula (not iron fortified)
- Teenage girls
  - ~11% prevalence of iron deficiency (5% with IDA)
  - Failure to benefit from universal lab screening (questionnaires poorly correlate with ID and anemia in adolescent girls)

Etiologies of iron deficiency

1. In adequate iron endowment at birth
2. Inadequate iron requirements (infants/adolescents)
3. Insufficient dietary iron
4. Inadequate iron absorption
5. Excessive blood loss
6. Functional inaccessibility of iron

Etiologies of iron deficiency

1. In adequate iron endowment at birth
2. Inadequate iron requirements (infants/adolescents)
3. Insufficient dietary iron
4. Inadequate iron absorption
5. Excessive blood loss
6. Functional inaccessibility of iron

Iron Requirements @ Birth (endowment)

- Dependent upon:
  - Birth weight (75 mg/kg) ~ 300 mg
    - Total body iron content is 4g in men and 3g in women
  - Hemoglobin concentration at birth (75-80% of iron in circulating RBC mass)
- Somewhat dependent on maternal iron status – iron transferred during 3rd trimester from mother to fetus
  - Suboptimal maternal iron status can also contribute to iron deficiency during neonatal period

- Depleted iron stores occurs in infants receiving no dietary by:
  - Age 5-6 months in term infants (in term infants iron deficiency uncommon <6 months of age)
  - Age 3 months in low BW infants or premature who has lesser iron endowment and grow at faster rate

Etiologies of iron deficiency

1. In adequate iron endowment at birth
2. Inadequate iron requirements (infants/adolescents)
3. Insufficient dietary iron
4. Inadequate iron absorption
5. Excessive blood loss
6. Functional inaccessibility of iron

Iron Requirements @ Infancy

- Normal term infants requirement = 1mg/kg/day
  - Breast milk have 50% bioavailability
  - Iron fortified formulas have 5-10% bioavailability
- Who needs “extra” iron? (2-3 mg/kg/day)
  - Premature or other LBW infants
  - Neonate with anemia proven
  - Suspected to be secondary to external blood loss

Iron Requirements @ Infancy: Prevention

- Breast feeding for at least the first 6 months of life
- Avoid cow milk before 12 months
- Limit cow milk intake to 18-24 oz daily after 12 months

- Iron fortified formulas
- Iron fortified infant cereals

- Medicinal iron for “high risk” infants

Parents.com

Iron Requirements @ Infancy: Food Iron Content

Milk	Iron content
• Breast	0.5-1 mg/Liter ** (more bioavailable)
• Whole Cow	0.5-1 mg/Liter
• Skim	0.5-1 mg/Liter
• Formula (low iron)	2-4 mg/Liter
• Formula (high iron)	10-12 mg/Liter

Semisolid Foods	
• Instant cereal	6 mg/serving
• Pureed foods	0.3-1.2 mg/serving

Iron Requirements Per Age

Elemental Iron Supplementation or Requirement in Children

AGE	IRON SUPPLEMENTATION OR REQUIREMENT
Preterm (< 37 weeks' gestation) infants: 1 to 12 months	2 mg per kg per day supplementation if exclusively breastfed
	1 mg per kg per day supplementation if using iron-fortified formula
Term infants: 4 to 6 months to 12 months	1 mg per kg per day supplementation if exclusively breastfed
	Supplementation not needed if using iron-fortified formula
Toddlers 1 to 3 years	Requires 7 mg per day; modify diet and/or supplement if anemic
Children 4 to 8 years	Requires 10 mg per day; modify diet and/or supplement if anemic

Wang M, *Am Fam Physician*. 2016

Etiologies of iron deficiency

1. In adequate iron endowment at birth
2. Inadequate iron requirements (infants/adolescents)
3. Insufficient dietary iron
4. Inadequate iron absorption
5. Excessive blood loss
6. Functional inaccessibility of iron

Etiologies of Iron deficiency: Insufficient Dietary Intake- Iron rich foods

<u>Heme Iron</u>

- Meat (esp beef and turkey)
- Shellfish

<u>Non-heme iron</u>

- Enriched breakfast cereal
- Enriched pasta
- Cooked beans & lentils
- Pumpkin seeds
- Canned beans
- Canned asparagus
- Baked potato with skin

Absorption <u>enhancers</u> (for non-heme iron): breast milk, fruits (vitamin C), meat/fish/poultry, white wine

Absorption depressed by: vegetable fiber, phytates, phosphates, tea/tannins, egg yolk, cow's milk

Intake of iron rich foods help prevent iron deficiency, but is not usually adequate to treat it

Why does excessive cow milk intake predispose to iron deficiency during infancy?

"Friends" NBC.com

- Contains minimal iron (<1 mg/L)
- Iron poorly absorbed (5-10% bioavailablility) compared to breast milk (50% bioavailability)
- Milk fills you up! → Leads to reduction intake of other foods and medicinal iron
  - i.e. blocks absorption of other iron-rich foods
- May cause GI bleeding
  - 40% of normal infants during feeding of cow's milk

"cow's milk is for calves, not for babies"

Etiologies of iron deficiency

1. In adequate iron endowment at birth
2. Inadequate iron requirements (infants/adolescents)
3. Insufficient dietary iron
4. Inadequate iron absorption
5. Excessive blood loss
6. Functional inaccessibility of iron

Etiologies of Iron deficiency: Malabsorption of Iron

Poor bioavailability

- Heme Fe > Fe2+ > Fe 3+
- Cow milk (infants/toddlers)
- Inhibitors of absorption
  - Bran, tannins, phytates, starch
  - Other metals (Co, Pb)
- High pH - inability to reduce non-heme iron from Ferric (+3) to preferred ferrous (+2) form
  - Antacids
  - Gastrectomy

Absorptive surface loss/dysfunction

- Duodenectomy
- Celiac disease (Gluten-sensitive enteropathy)
- Inflammation

How to check for malabsorption?

Screen by oral iron challenge (serum iron level before and 2 hours after 1mg/kg oral iron)

Etiologies of iron deficiency

1. In adequate iron endowment at birth
2. Inadequate iron requirements (infants/adolescents)
3. Insufficient dietary iron
4. Inadequate iron absorption
5. Excessive blood loss
6. Functional inaccessibility of iron

Etiologies of Iron deficiency: Excessive Blood Loss

- Recurrent prolonged epistaxis
- Menorrhagia

} Check for bleeding disorder!

- Pregnancy
- GI tract blood loss
  - Whole cow milk – "dose related", not allergic
  - Parasitic infections (hookworm, whipworm)
  - H. pylori infection
  - Esophageal varices (portal hypertension)
  - Other anatomy lesions (Meckel's diverticulum, duplication, ulcers)
  - Inflammatory bowel disease
  - "Sports anemia"
- Intrapulmonary or renal loss (rare)
  - Idiopathic pulmonary hemosiderosis
  - Chronic intravascular hemolysis
  - "Sports anemia"
  - Renal cell carcinoma
  - Glomerulonephritis
- Frequent blood donation

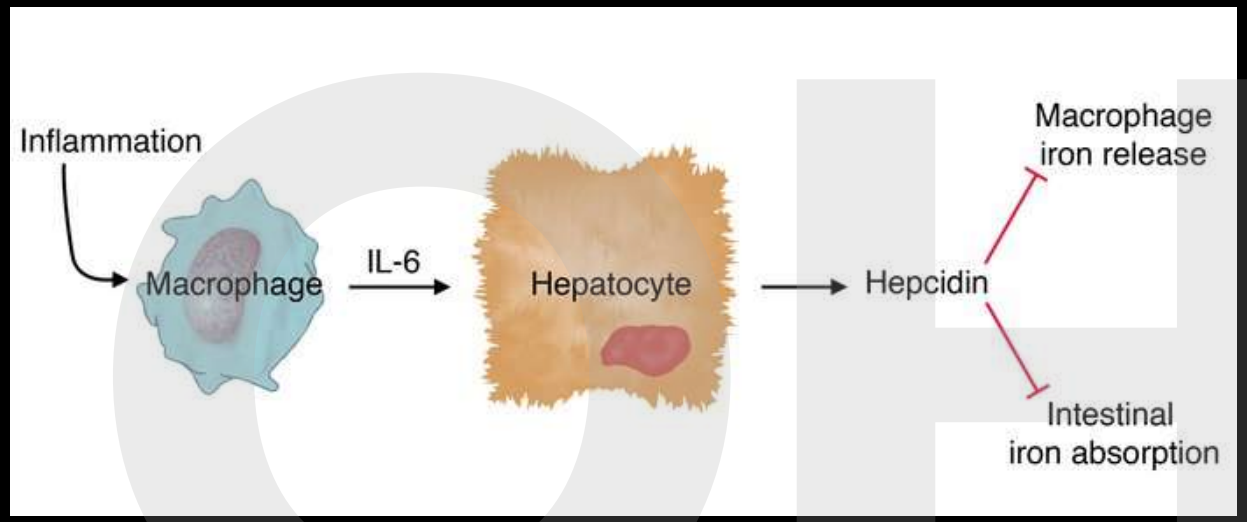
“Sports anemia”

- 22% marathoners with guaiac positive stool after marathon
  - Inflammation
  - Gastritis
  - “Jarring” of bowel (although seen in swimmers/skaters)
  - Ischemia
  - Dehydration
  - Hemolysis from foot strike/contraction
- Labeled iron studies show persistent blood loss of 1.5 ml/day with increase up to 5-6 ml/day with training

Etiologies of iron deficiency

1. In adequate iron endowment at birth
2. Inadequate iron requirements (infants/adolescents)
3. Insufficient dietary iron
4. Inadequate iron absorption
5. Excessive blood loss
6. Functional inaccessibility of iron

Etiologies of Iron deficiency: Functional Inaccessibility



Andrews NC, *J Clin Invest*. 2004

Elevated hepcidin → sequesters iron in RE system and duodenal enterocyte

- Anemic of Chronic Inflammation/Disease/Infection
  - Common. Acquired
  - Role in innate immune response?
  - Mediated by inflammatory cytokines (e.g. IL-6)
- Iron Refractory Iron Deficiency Anemia (IRIDA)
  - Rare. Inherited.
  - Mediated by mutations in TMPRSS6

Iron Refractory Iron Deficiency Anemia (IRIDA)

- Key clinical features:
  - Congenital onset
  - Severe microcytosis (MCV 50-60 fL)
  - Iron deficiency not responsive to oral iron therapy
    - Fail oral iron challenge test
  - “Sluggish” and incomplete response to parenteral iron
  - Other causes of microcytosis meticulously excluded

May 1981
The Journal of PEDIATRICS

Malabsorption and defective utilization of iron in three siblings

Three siblings had iron deficiency anemia without evidence of reduced iron intake or gastrointestinal blood loss. They failed to respond to oral iron therapy, and malabsorption of oral medicinal iron was demonstrated in two of the children. All three had a partial but incomplete hematologic response to intramuscular iron dextran treatment. There was no evidence for other well-defined causes of hypochromic microcytic anemia or for a generalized disorder of intestinal absorption. These three patients appear to have a familial disorder characterized by impaired iron absorption and utilization, similar to that observed in the mk/mk *mouse.*

George R. Buchanan, M.D.,* and Richard G. Sheehan, M.D., *Dallas, Texas*

Part III: Diagnosing Iron Deficiency

Diagnosis of Iron Deficiency

History

- Diet, sources and characteristics of potential bleeding, malabsorption, inflammation
- Symptoms: irritability, fatigue, decreased activity, pallor, pica

https://en.wikipedia.org/wiki/Hulk

Physical Examination

- Non-specific findings of anemia: tachycardia, heart murmur, pallor
  - absence of jaundice and hepatosplenomegaly
- “Specific” abnormalities (rarely seen in children):
  - koilonychia, chlorosis, esophageal webs, etc

www.msdmanuals.com/

Laboratory evaluation

Iron deficiency and pica

- Intense craving for an ingestion of a non-food item
- Common characteristics: single item, crunchy, compulsive behavior cured with therapeutic iron

Rocks
Dirt
Paint chips
Paper (tissue or other)
Cardboard
Insects
Hair
Clay
Starch

Carrots
Ice cubes (pagophagia)
Celery
Clothing
Baby wipes
Cornstartch
Laundry detergent/soap

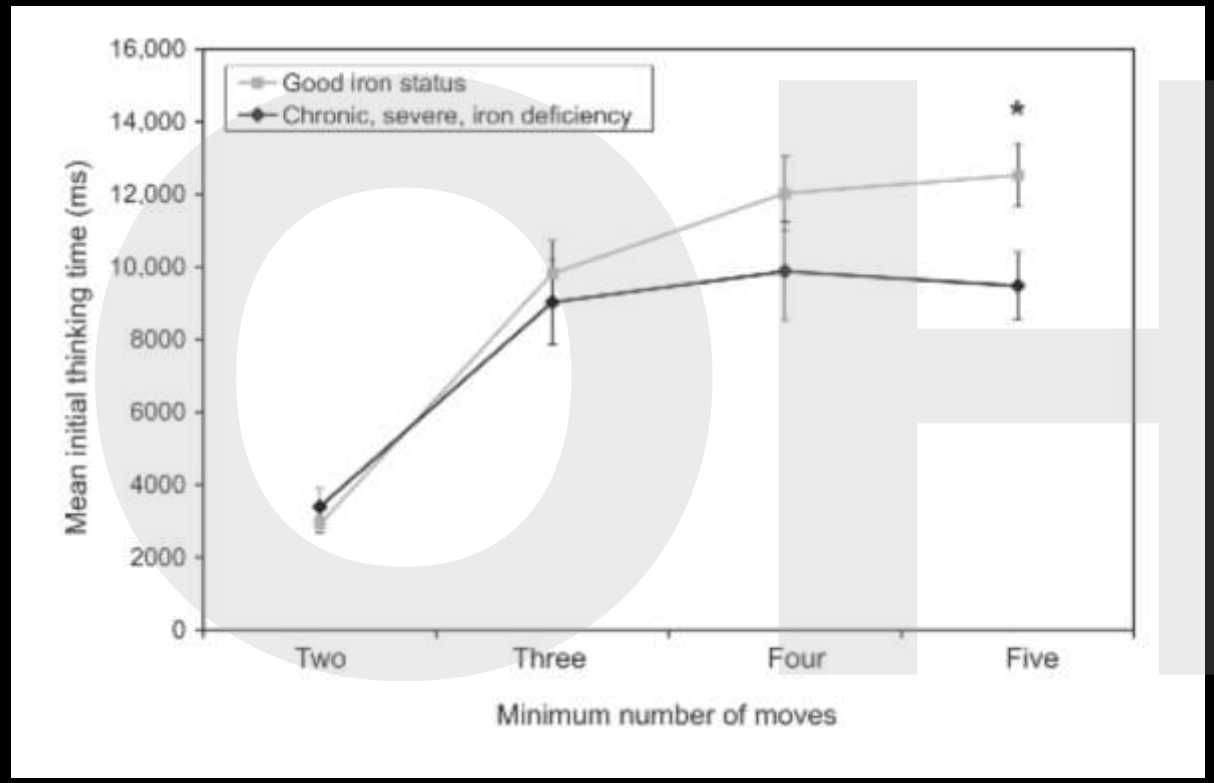
Iron deficiency and pica

Powers JM et al, Hematol/Oncol Clinics of North America 2019

Iron Deficiency: Non-hematologic Effects

- Fatigue!
- Pica
- Breath-holding spells
- Restless leg syndrome
- Dry mouth/cheilitis, atrophic glossitis
- Decreased work performance
- Impaired cardiac function
- Stroke
- Alopecia
- Pulmonary HTN
- Acute mountain sickness
- Reduced cognition
  - Infants and young children
  - May persist into young adulthood
  - Only partially reversible
- Biochemical alterations
  - Neurotransmitter metabolism
  - Energy metabolism
  - Impaired myelination

Iron deficiency: Non-hematologic Effects→ neuro-cognitive



normal iron

low iron

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/only partially reversible

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

Iron deficiency: Non-hematologic Effects→ neuro-cognitive

TABLE 4. Percentage of Children Scoring Below Average by Iron Status

	Normal Iron Status (%)	Iron-Deficient Without Anemia (%)	Iron-Deficient With Anemia (%)
Math	49	71*	72
Reading	46	47	51
Block design	48	50	50
Digit span	46	47	48

$P < .01$ for difference compared with children with normal iron status by χ^2 analysis.

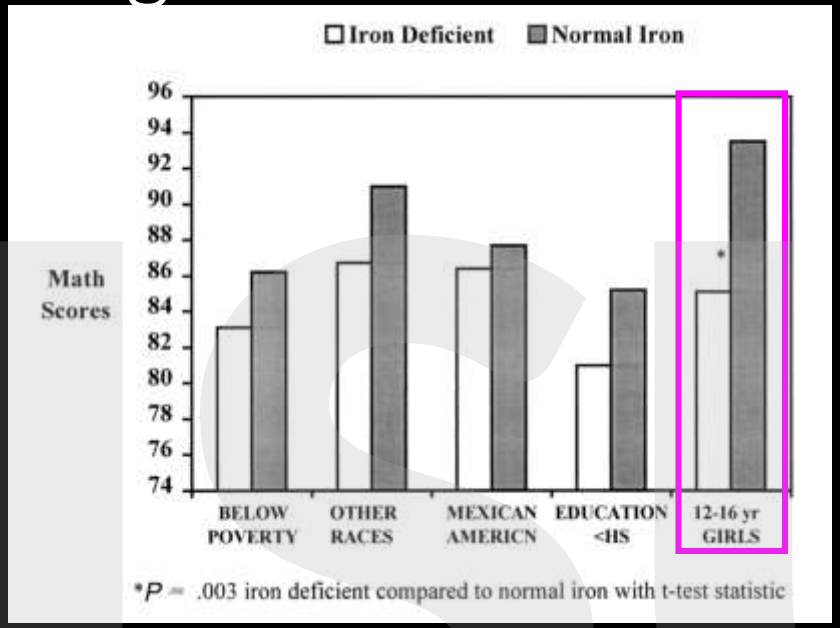


TABLE 2. Prevalence of Iron Deficiency by Demographic Patient Characteristics

Demographic Characteristic	*n*	Iron-Deficient Without Anemia (%)	Iron-Deficient With Anemia (%)	Iron-Deficient Total (%)
Age 6–11 y				
Females	1617	2.0	0.1	2.1
Males	1692	1.3	0.2	1.5
Age 12–16 y				
Females	1114	7.2	1.5	8.7
Males	975	0.8	0.1	0.9
Race				
White	1402	2.0	0.3	2.3
Black	1875	1.8	1.3	3.1
Mexican American	1874	5.3	0.8	6.1
Other	247	5.8	0.1	5.9
Poverty status				
Below poverty	1967	4.7	0.7	5.4
Above poverty	2991	1.8	0.4	2.2
Caretaker education				
<12th grade	2227	3.4	0.4	3.8
12th grade	1715	2.6	0.7	3.3
>12th grade	1417	2.2	0.3	2.5

- 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.

- Meta-analysis of 32 studies of 7,089 children
- Most studies in low/middle income settings
- Iron supplements
  - Improved global cognitive scores
  - IQ in anemic children
  - Height
  - Weight in anemic children

Screening for Iron Deficiency Anemia in Young Children: USPSTF Recommendation Statement

Albert L. Siu, MD, MSPH, on behalf of the US Preventive Services Task Force

abstract

DESCRIPTION: Update of the US Preventive Services Task Force (USPSTF) 2006 recommendation on screening for iron deficiency anemia.

METHODS: The USPSTF reviewed the evidence on the association between change in iron status as a result of intervention and improvement in child health outcomes, as well as screening for and treatment of iron deficiency anemia with oral iron formulations, in children ages 6 to 24 months.

POPULATION: This recommendation applies to children ages 6 to 24 months living in the United States who are asymptomatic for iron deficiency anemia. It does not apply to children younger than age 6 months or older than 24 months, children who are severely malnourished, children who were born prematurely or with low birth weight, or children who have symptoms of iron deficiency anemia.

RECOMMENDATION: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for iron deficiency anemia in children ages 6 to 24 months. (I statement)

FREE

www.pediatrics.org/cgi/doi/10.1542/peds.2015-2567

Albert L. Siu, Pediatrics Oct 2015,

- No studies directly evaluated the effectiveness of screening for iron deficiency anemia in asymptomatic children ages 6 to 24 months and reported on health outcomes.
- There is poor evidence (conflicting studies) of effectiveness of interventions that demonstrate improve health outcomes

Iron deficiency: other non-hematologic effects

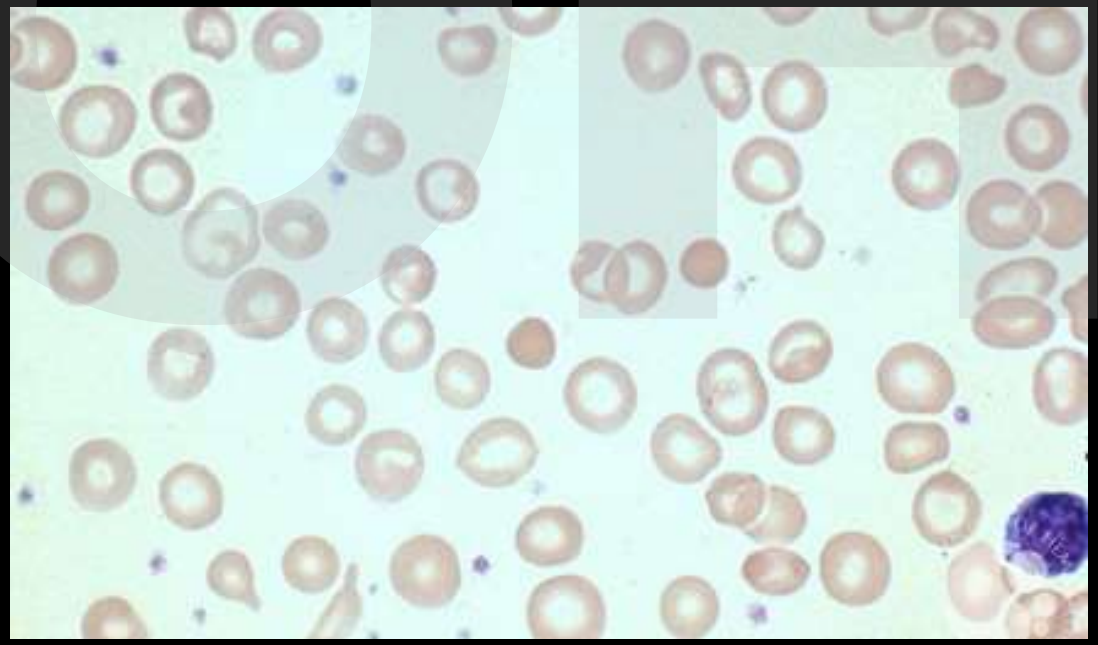
- Quality if life: In women with heavy menstrual bleeding, iron deficiency is associated with lower Health Related Quality of Life scores
- Fatigue: associated with lower ferritin levels (with or without anemia); iron improves fatigue stores if ferritin <50 ng/mL
- Exercise: effects maximal exercise ability, endurance, strength, cold tolerance; low iron inhibits performance
- Behavioral/psych: a higher risk of depression, bipolar disorder, anxiety, autism, developmental delay, and attention deficit hyperactivity disorder

Houston BL, et al. BMJ Open. 2018 (8)
BMJ. 2003 May 24;326(7399):1124.
Peuranpaa P, et al. ACTA Obstetricia et Gynecologicia. 2014 (93): 654-660.
Chen M, et al. BMC Psychiatry. 2013 (13): 1-8.

Laboratory Evaluation of Iron status

- 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)]

= 2 SD below mean



imagebank.hematology.org/image/60219/iron-deficiency-anemia-moderate

Microcytic anemia during childhood

- Most common:
  - Iron deficiency
  - Thalassemia
  - Anemia of inflammation
- Less common:
  - Hemoglobin C disease
  - Hemoglobin E disease
- Rare:
  - Hereditary pyropoikilocytosis
  - Sideroblastic anemia
  - Copper deficiency
  - Congenital atransferrinemia

Stages of Iron Deficiency that lead to Anemia

	Normal	Prelatent Iron Deficiency	Latent Iron Deficiency	Iron Deficiency Anemia
Iron stores	Present	Decreased	Absent	Absent
Ferritin (ng/mL)	>40	<20	<10	<10
TF saturation (%)	35	35	<16	<16
Free erythrocyte protoporphyrin	10	10	>35	>35
Hemoglobin (g/dL)	12	12	12	<11
MCV (fL)	80	80	80	<70

Heeney M, Rudolph's Pediatrics 2011 from 2017 ASPHO Review Course

The best "test" for iron deficiency anemia is complete resolution of anemia following a therapeutic trial of iron

Laboratory Evaluation of Iron status- no perfect test!

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

Lacks sensitivity/specificity

An acute phase reactant

Specific but not sensitive

Varies wildly

Low in both ID AND ACD

** Bone marrow tests

Which non-invasive iron test is best?

Review: Serum ferritin radioimmunoassay is the most accurate test for determining iron-deficiency anemia

ACP J Club. 1992 July-Aug;117:23. doi:10.7326/ACPJC-1992-117-1-023

Source Citation

Guyatt GH, Oxman AD, Ali M, et al. **Laboratory diagnosis of iron-deficiency anemia: an overview.** J Gen Intern Med. 1992 Mar-Apr;7:145-53.

- Ferritin is the best non-invasive test of iron status
- Laboratory cut-off not optimal (changes with age/condition)
  - Ferritin > 100 ng/mL rule-out iron deficiency
  - Mild iron deficiency = <30 ng/mL
  - Ferritin <15 ng/mL are 100% specific for iron deficiency

Other labs suggestive of Iron deficiency

- Platelet count ↑
- Zinc protoporphyrin ↑
- RDW ↑
- Hemoglobin A2 ↓
- Hepcidin ↓
- Serum transferrin receptor (sTfR) ↑
- Erythroferrone (ERFE) ↑

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

Screening for Iron deficiency anemia

- CDC: 9-12 mo, 6 mo later, then annually from 2-5 yo in high-risk
- IOM: 9 mo in FT; 3 mo preterm; if anemic 15-18 mo recheck
- AAP (since early 1970s): Term infants: 12 months; Pre-term infants: 6-9 months
- AAFP, USPSTF: insufficient evidence for risk/benefits of screening

- May not be necessary in healthy infants receiving iron supplementation
- Assess for risk factors (low birthweight, prolonged breast feeding, excessive whole cow milk intake, bleeding, etc)
- Screening for anemia with a Hb neither identifies children with iron deficiency nor specifically identifies iron deficiency anemia
- In the US, 60% of anemia is not attributable to iron deficiency and most toddlers with ID do not have anemia

Part III:
Treatment options of iron deficiency

Treatment of iron deficiency

- Principle:
  - Identify and eliminate cause
  - Replace hemoglobin iron deficit and replete iron stores
- Few comparative studies of optimal iron preparations, doses, and schedules
- Administer elemental iron:
  - 3 mg/kg as single dose when mild
  - 4-6 mg/kg in 2 divided doses when severe
  - 2-3 mg/kg for adolescents
- PRBC transfusion reserved for severe cases (Hb <4 g/dL), followed by oral iron

All Iron Formulations are Not Equal

- Amount of iron per dose
- Volume of liquid/size of tablet
- Taste
- Absorption
- Cost
- Description on label (“supplement”)
- Likelihood of adherence

Oral Iron Formulations

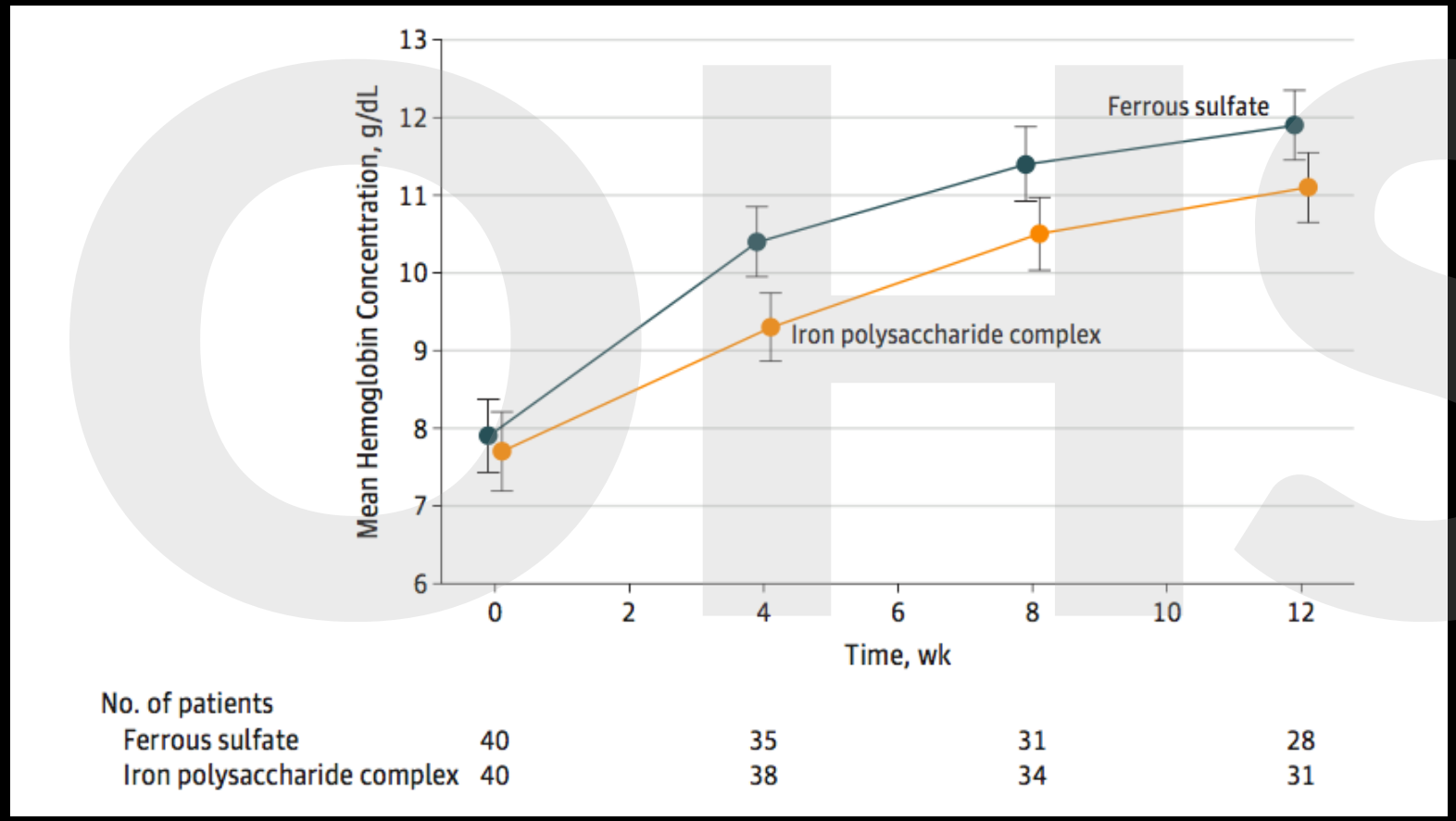
- Enfamil ®
- Fer-in-sol ®
- Feosol ® Iron supply therapy
- FERO-GRAD-500 ®
- NovaFerrum ® Liquid iron
- Niferex-150 ®
- Icar ® Pediatric Suspension
- NulronV 150 ®
- Femiron ®

All iron formulations are not equal

- Iron salt: sulfate, gluconate, fumarate
- Iron polysaccharide: Niferex®, Novaferrum ®
- Carbonyl iron (small particles <5um diameter): ICAR®

- Dozens of preparations available by prescription and OTC
- Many of them are costly and/or are not well tolerated

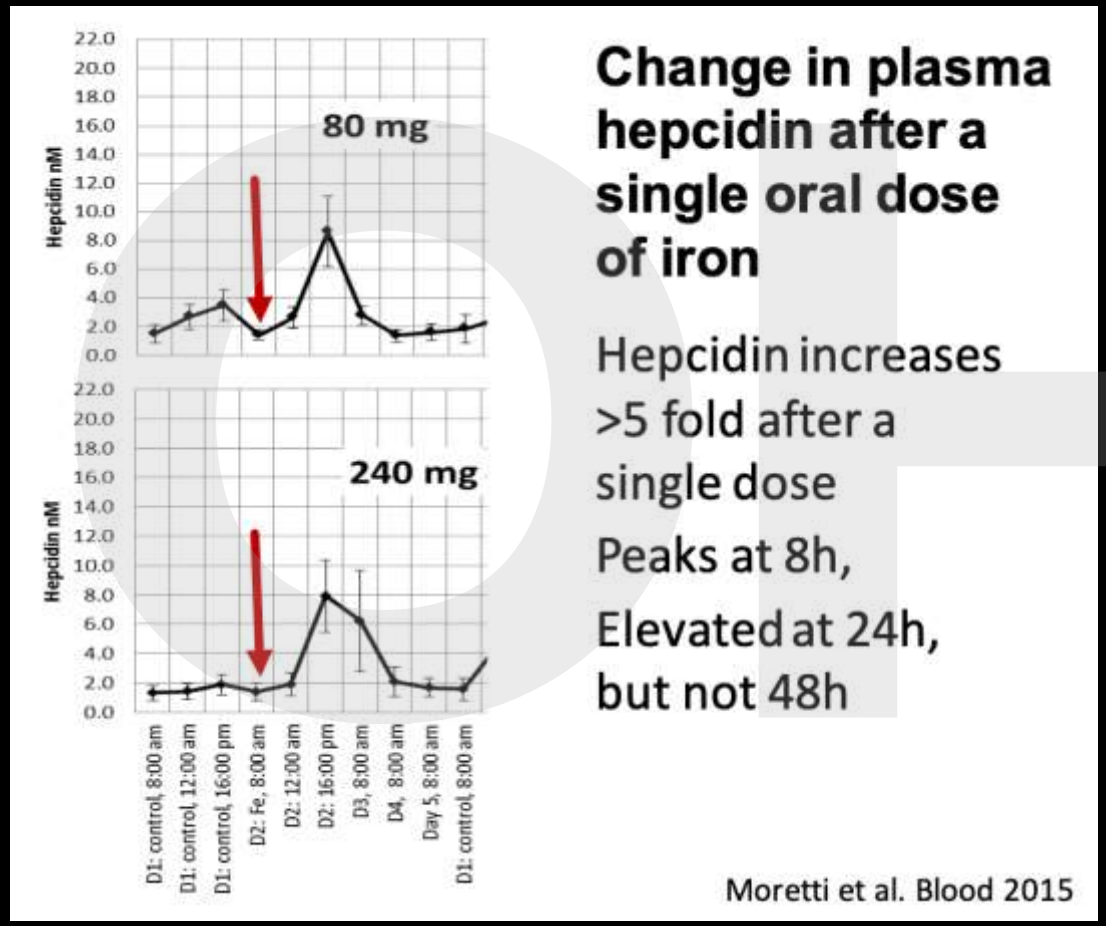
Iron deficiency: Ferrous sulfate? Polysacchide?



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

- 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

Iron deficiency: Dosing



Change in plasma hepcidin after a single oral dose of iron

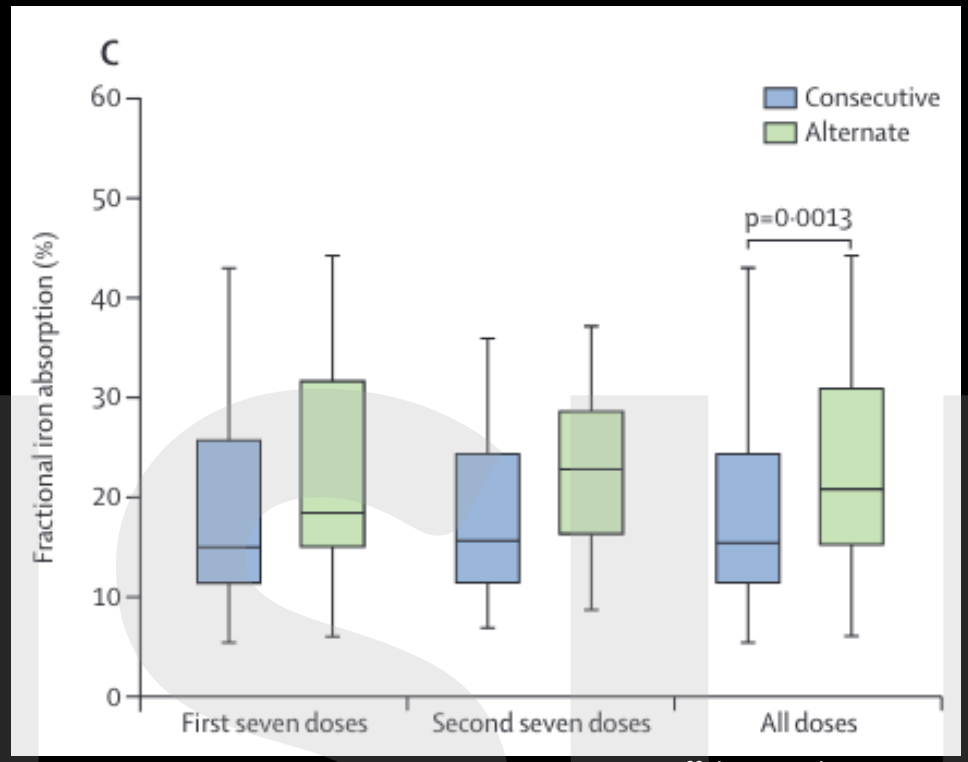
Hepcidin increases >5 fold after a single dose

Peaks at 8h,

Elevated at 24h, but not 48h

Moretti et al. Blood 2015

Take-home point: Give as a single dose – no dividing!



Stoffel NU et al, Lancet 2017

Take-home point: alternate day dosing OK!

CLINICAL RESEARCH STUDY

Are we giving too much iron? Low-dose iron therapy is effective in octogenarians

Ephraim Rimon, MD, Nadya Kagansky, MD, Michael Kagansky, MD, Lora Mechnick, MD, Tony Mashiah, MD, Michael Namir, MD, Shmuel Levy, MD

Geriatric Department, Kaplan Medical Center, Rehovot, and the Hebrew University and Hadassah Medical School, Jerusalem, Israel.

Take-home point: lower doses of Iron OK!

Iron deficiency: oral iron – our recommendations

- Iron deficient:
  - In infants and children: 3 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/coffee, or cow's milk
- Use whatever preparation results in the patient taking their iron

Monitoring Iron Therapy

- 1-2 weeks after start (in moderate-severe cases only): document rise in reticulocyte count and hemoglobin (>> 1-2 g/dL)
- 2-3 months (all patients): document complete correction of anemia
- 4 months (all patients): iron stores should be replenished
  - ? Goal: ferritin 50-100 ng/mL

- Duration of treatment : at least 3 months
  - at least 1 month after correction of anemia to assure repletion of iron stores
  - Assess ferritin level before discontinuing

- Monitor for toxicity/adherence:
  - GI intolerance (nausea, constipation/diarrhea, adversely altered GI microbiome, gastritis)
  - Dark stools
  - Stained teeth
  - Bad taste

Reasons for Poor Response to Oral Iron Therapy

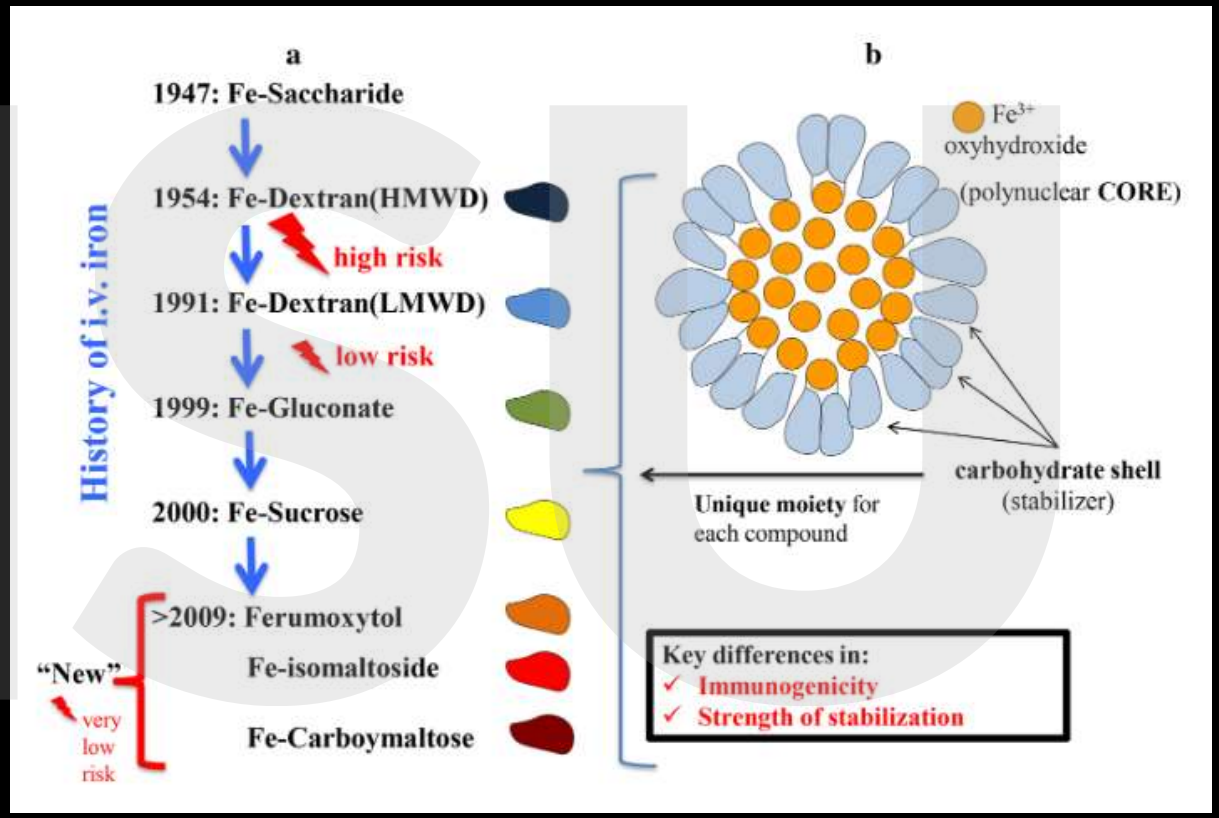
- Incorrect dose of iron (common)
- Parents not administering iron according to instructions (very common)
- Patients not taking it (very common)
- Child is malabsorbing iron (Uncommon):
  - underling GI disorder, concomitant inflammatory condition, administration of oral iron with milk
- Ongoing blood loss (occasionally)
- Incorrect diagnosis -- child doesn’t have iron deficiency (common)

Reasons for lower adherence to oral iron therapy

- Adverse effects (real or perceived)
- Lengthy course of required (3 months+)
- Troublesome once or twice daily dosing
- Multiple prescription refills required to complete course
- Forgetting or refusing to take medication
- “Well” patient taking medication on a daily basis for prolonged period of time

Parenteral Iron Formulations

- All current IV iron products are iron-carbohydrate complexes or colloids
- They differ by the size of the core, and the identify and density of the carbohydrate shell
- Side effects:
  - Mild/mod (~1:200): Back/joint pain, flushing, HTN, itching, chest tightness, urticaria, cough, dyspnea, hypotension, tachycardia, complement activation-related pseudoallergy, hypophosphatemia
  - Severe (<1:200,000): Cardiac arrest, cyanosis, LOC, periorbital edema, wheezing/stridor
- Data on the use of IV iron in pediatrics is sparse



Girelli, D., Ugolini, S., Busti, F. et al. Int J Hematol (2018)

Parenteral Iron Formulations

- INFeD ® = iron dextran injection
- Ferrlecit ® = sodium ferric gluconate complex in sucrose
- Feraheme ® = ferumoxytol injection
- MonoFer ® = Iron isomaltoside
- Injectafer ® = Ferric carboxymaltose Injection
- Venofer ® = iron sucrose Injection

When to Consider Parenteral Iron Therapy

- Iron deficiency not responding to oral iron, due to :
  - Poor adherence
  - Adverse effects
  - Malabsorption
  - No change in iron parameters after 3 months oral iron
  - Severe anemia
  - Ongoing hemorrhage (menstruation, GI disorders)

- Functional iron deficiency (iron-restricted erythropoiesis) due to:
  - Chronic renal failure
  - Cancer
  - Inflammatory disorders
  - Iron refractory iron deficiency anemia (IRIDA)

- Patient and family understand risk of adverse events

Iron deficiency: General recommendations to PCPs

- 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!
- Tell them if they don't get better, to send them over so we can either:
  - 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 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 and have other non-hematologic symptoms
- Treatment of iron deficiency can be difficult
- IV iron isn’t as scary as it used to be

Thank you!

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

- Nancy Andrews, Christina Ulrich, and Mark Fleming

Contact: Melinda Wu: wume@ohsu.edu