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
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.
Iron status is regulated entirely at the level of absorption!

- 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 ferritin
  4. FPN1 exports Fe2+ at the basolateral side to then bind to transferrin (Tf)

Donovan, Adriana et al. Physiology, 2006
Systemic Iron Regulation: Macrophage Recycling

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
Hepcidin: the iron regulatory hormone

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

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Hepcidin Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>↓</td>
</tr>
<tr>
<td>Iron overload</td>
<td>↑↑</td>
</tr>
<tr>
<td>Increased erythroid demand</td>
<td>↓</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>↓</td>
</tr>
<tr>
<td>Inflammation</td>
<td>↑</td>
</tr>
</tbody>
</table>
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
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. Inadequate 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. Inadequate iron endowment at birth
2. Inadequate iron requirements (infants/adolescents)
3. Insufficient dietary iron
4. Inadequate iron absorption
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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
Iron Requirements @ Infancy: Food Iron Content

<table>
<thead>
<tr>
<th>Milk</th>
<th>Iron content</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Breast</td>
<td>0.5-1 mg/Liter ** (more bioavailable)</td>
</tr>
<tr>
<td>• Whole Cow</td>
<td>0.5-1 mg/Liter</td>
</tr>
<tr>
<td>• Skim</td>
<td>0.5-1 mg/Liter</td>
</tr>
<tr>
<td>• Formula (low iron)</td>
<td>2-4 mg/Liter</td>
</tr>
<tr>
<td>• Formula (high iron)</td>
<td>10-12 mg/Liter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Semisolid Foods</th>
<th>Iron content</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Instant cereal</td>
<td>6 mg/serving</td>
</tr>
<tr>
<td>• Pureed foods</td>
<td>0.3-1.2 mg/serving</td>
</tr>
</tbody>
</table>
# Iron Requirements Per Age

## Elemental Iron Supplementation or Requirement in Children

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

Etiologies of iron deficiency

1. Inadequate 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

Heme Iron
- Meat (esp beef and turkey)
- Shellfish

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

Absorption enhancers (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?

- Contains minimal iron (<1 mg/L)
- Iron poorly absorbed (5-10% bioavailability) 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. Inadequate iron endowment at birth
2. Inadequate iron requirements (infants/adolescents)
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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. Inadequate 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
- 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

Check for bleeding disorder!
“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. Inadequate iron endowment at birth
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Etiologies of Iron deficiency: Functional Inaccessibility

Elevated hepcidin $\rightarrow$ 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
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

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

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
Cornstarch
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

- Infants and young children may persist into young adulthood only partially reversible.
- Biochemical alterations include neurotransmitter metabolism, energy metabolism, and impaired myelination.
Iron deficiency: Non-hematologic Effects ➔ neuro-cognitive

- 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.

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.

Iron deficiency: Non-hematologic Effects ➔ neuro-cognitive

Iron deficiency was defined as ferritin < 12. Iron deficiency anemia was defined as ferritin < 12 and hemoglobin < 5% for age.

- 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.

Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials

Michael Low MBBS BMedSci, Ann Farrell MBBS, Beverley-Ann Biggs PhD, Sant-Rayn Pasricha PhD

- 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

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)

- 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 of 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.

BMJ. 2003 May 24;326(7399):1124.
Laboratory Evaluation of Iron status

• CBC: microcytic, hypochromic anemia
  • Lower limit of normal hemoglobin: $11 + [0.1 \times (\text{age in years})]$
  • Lower limit of normal MCV: $70 + [1 \times (\text{age in years})]$

= 2 SD below mean
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

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Prelatent Iron Deficiency</th>
<th>Latent Iron Deficiency</th>
<th>Iron Deficiency Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron stores</td>
<td>Present</td>
<td>Decreased</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>&gt;40</td>
<td>&lt;20</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>TF saturation (%)</td>
<td>35</td>
<td>35</td>
<td>&lt;16</td>
<td>&lt;16</td>
</tr>
<tr>
<td>Free erythrocyte protoporphyrin</td>
<td>10</td>
<td>10</td>
<td>&gt;35</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>&lt;11</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

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!

<table>
<thead>
<tr>
<th>Lab</th>
<th>Iron Deficiency</th>
<th>Thalasemia</th>
<th>Anemia of chronic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>Decreased or normal if early</td>
<td>Normal in trait, can be severely low in major</td>
<td>Normal to slightly decreased</td>
</tr>
<tr>
<td>MCV</td>
<td>Low</td>
<td>Very low</td>
<td>Low to normal</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Decreased</td>
<td>Normal to Increased</td>
<td>Normal to Increased</td>
</tr>
<tr>
<td>TIBC</td>
<td>Increased</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Serum Iron</td>
<td>Decreased to normal</td>
<td>Normal to increased</td>
<td>Decreased to normal</td>
</tr>
<tr>
<td>Transferrin Saturation</td>
<td>Decreased</td>
<td>Normal to increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

- ** Bone marrow tests
- Lacks sensitivity/specificity
- An acute phase reactant
- Specific but not sensitive
- Varies wildly
- Low in both ID AND ACD
Which non-invasive iron test is best?

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


Source Citation

• 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? Polysacchride?

- 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!

Take-home point: alternate day dosing OK!

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, Kupat Holim Medical Center, Rehovot, and the Hebrew University 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):
  • underlying 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
Parenteral Iron Formulations

- INFeD® = iron dextran injection
- Ferrlecit® = sodium ferric gluconate complex in sucrose
- Feraheeme® = 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

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