Iron Deficiency and Overload
Victor Gordeuk, MD

Disclosures
Disclosures of Financial Relationships with Relevant Commercial Interests
- Grant support: CSL Behring, Global Blood Therapeutics, Imara, Ironwood, Novartis
- Consulting: CSL Behring, Global Blood Therapeutics, Novartis, Forma

Outline
1. Review of iron metabolism
2. Iron deficiency
3. Iron overload: hereditary, environmental, transfusional

Iron
- Essential nutrient for all living organisms.
  - Reversible binding of O₂: Hb, myoglobin
  - Enzyme systems:
    - heme (cytochromes, catalase, glutathione peroxidase, NO synthase)
    - non-heme (RNR, aconitase)
  - Immunity: free radicals to destroy microbes
  - Highly reactive with O₂: can cause toxicity

Iron Metabolism: Broad Themes
- Deficiency of iron
  - most common nutritional problem worldwide
- Iron overload
  - less common
  - important health problem
- Absorption of iron
  - highly regulated to prevent excess Fe from being absorbed
- Excretion of iron
  - There is no physiologic pathway for excreting excess iron

Iron Requirements
<table>
<thead>
<tr>
<th>Obligatory losses</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total losses</td>
<td>1.0 mg/d</td>
<td>1.5 mg/d</td>
</tr>
<tr>
<td>Iron absorbed</td>
<td>1.0 mg/d</td>
<td>1.5 mg/d</td>
</tr>
</tbody>
</table>

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Thursday, August 13, 2020

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Body Iron Compartments

<table>
<thead>
<tr>
<th></th>
<th>65 kg F</th>
<th>75 kg M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1900 mg</td>
<td>2500 mg</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>310 mg</td>
<td>340 mg</td>
</tr>
<tr>
<td>Enzymes</td>
<td>170 mg</td>
<td>190 mg</td>
</tr>
<tr>
<td>Transferrin</td>
<td>2.7 mg</td>
<td>3.2 mg</td>
</tr>
<tr>
<td><strong>Storage compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>300 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Total</td>
<td>~2700 mg</td>
<td>~3800 mg</td>
</tr>
</tbody>
</table>

Simplified Diagram of Iron Movement in the Body

Dietary Iron

- Typical diet men
  - Mean of 18 mg/day
  - SD range of 4 - 30 mg/day
- Typical diet women
  - Mean of 13 mg/day
  - SD range of 7 - 19 mg/day
- ~1/3 of Fe from fortification of flour

Iron absorption- proximal small bowel

Hepcidin- 25 aa peptide produced by liver that suppresses iron absorption

Enhanced absorption
- Low hepcidin:
  - Iron deficiency
  - erythropoiesis
- Dietary factors:
  - ascorbic acid (Fe²⁺ valance absorbed)
  - Heme vs non-heme Fe

Inhibited absorption
- High hepcidin
  - ↑ iron stores
  - Inflammation
- Dietary factors:
  - tannins (tea)
  - phytates (bran)

Iron Transport into Plasma

Iron Entry into Erythroid Precursors

Duodenal Enterocyte

Adapted from Andrews, NEJM 1999;341:1986

What We Eat in America, NHANES 2007-2008
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### Changes in Indirect Indicators of Fe Status

- **Serum Fe & Tf Sat**
  - Iron deficiency
  - Inflammation
  - Diurnal variation
  - Blood drawn afternoon or evening

- **Serum Ferritin**
  - Iron deficiency

### Fe Deficiency anemia

- Microcytosis
- Central pallor

### Fe Deficiency anemia:

- Marked microcytosis
- Marked central pallor

### Fe Deficiency: Causes

1. **Chronic blood loss**
   - GI bleeding: ulcer, tumor, cancer, diverticuli, etc.
   - Heavy menses, menorrhagia
   - Frequent blood donation; hemodialysis
   - Hook worm infestation
2. **Increased physiologic requirements**
   - Women (menstruation, pregnancy, lactation)
   - Infants & adolescents (growth spurt)
3. **Decreased absorption**
   - Celiac disease (gluten enteropathy)
   - Autoimmune (atrophic) gastritis; *H. pylori*
   - Inflammatory bowel disease
   - Gastrectomy- loss of gastric acid
   - Duodenal bypass surgery

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Fe Deficiency: Causes
4. Hemoglobinuria (intravascular hemolysis)
   • PNH
   • Runners
   • Damaged heart valves
   • Microangiopathic hemolysis
5. Sequestration
   • Pulmonary alveolar bleeding in idiopathic pulmonary hemosiderosis or Goodpasture’s syndrome

Fe Deficiency: Causes
6. Genetic predisposition
   • TMPRSS6 mutations (Iron-refractory IDA - excessive production of hepcidin)

Iron-Refractory Iron Deficiency Anemia
• Severe autosomal recessive anemia
• Lack of response to oral Fe
• Partial response to IV Fe
• Several TMPRSS6 mutations implicated

Fe Deficiency: Clinical Manifestations
• Impaired psychomotor development
• Fatigue, irritability, ↓ work productivity
• Pica
• Koilonychia, glossitis, angular stomatitis
• Dysphagia 2° to esophageal web (Plummer-Vinson or Patterson-Kelly Sx)
• Increased risk of thrombosis

Fe Deficiency: Lab Findings
1. Peripheral blood cells
   • ↑ RDW, platelets
   • ↓ MCV, MCH, MCHC, RBC, Hb, Hct
   • Retics not increased
   • ↑ RBC protoporphyrin
2. Serum tests
   • ↓ Fe, Tf Sat, ferritin (< 12 µg/L)
   • ↑ TIBC, transferrin, transferrin receptor
3. Bone marrow aspirate
   • Absent macrophage Fe; ↓ sideroblasts
   • Erythroid hyperplasia
4. Other tests if blood loss not found
   • Autoimmune gastritis: ↑ gastrin, antiparietal cell ab +
   • Gluten enteropathy: anti-endomyoseal ab +
   • H. pylori: ab +, urease breath test +
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Fe Deficiency: Therapy

1. Oral
   - Ferrous sulfate: standard approach
     • 200 mg elemental Fe/d (3-325mg tabs/d)
     • 5.0 mg elemental Fe/kg per day in children
     • risk of iron poisoning
     • Once a day or alternate day dosing may be preferable

2. Intravenous
   - Iron dextran (INFeD)
   - Ferric gluconate complex in sucrose (FERRLECIT)
   - Iron sucrose (VENOFER)

   • Risk of hypersensitivity rexs: premedicate with steroid and antihistamine in patients at risk
   • Used successfully and safely during pregnancy

Other conditions with microcytosis (approximate Hb and MCV values)

<table>
<thead>
<tr>
<th></th>
<th>Hb</th>
<th>MCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia of inflammation</td>
<td>10</td>
<td>83</td>
</tr>
<tr>
<td>Thalassemia minor</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>2-7</td>
<td>48-72</td>
</tr>
<tr>
<td>Hb H disease</td>
<td>9</td>
<td>70</td>
</tr>
<tr>
<td>Hb E trait</td>
<td>14</td>
<td>73</td>
</tr>
<tr>
<td>Hb CC</td>
<td>10</td>
<td>74</td>
</tr>
<tr>
<td>Hb SC</td>
<td>11</td>
<td>78</td>
</tr>
<tr>
<td>Hereditary sideroblastic anemia</td>
<td>6</td>
<td>77</td>
</tr>
</tbody>
</table>

Ftn cutoffs of absent BM Fe in anemia associated with inflammation

<table>
<thead>
<tr>
<th>Ftn (ng/ml)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
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<tbody>
<tr>
<td>&lt;100</td>
<td>88-100%</td>
<td>46-64%</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;60</td>
<td>82-86%</td>
<td>84-88%</td>
<td>84%</td>
</tr>
<tr>
<td>&lt;50</td>
<td>74-82%</td>
<td>84-97%</td>
<td>88%</td>
</tr>
<tr>
<td>&lt;40</td>
<td>71%</td>
<td>98%</td>
<td>92%</td>
</tr>
<tr>
<td>&lt;12</td>
<td>24%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Punnonen et al. Blood 1997;89:1052
Kis and Cames, J Gen Int Med 1998:13:455
What is Iron Overload?

- Excessive amounts of storage iron
  - parenchymal cells: liver, heart, pancreas (HH)
  - macrophages: spleen, BM, liver (Txs)
  - mixed pattern
- Quantitative considerations
  - mild: 2-4 g; moderate: >4-10 g
  - marked: 10-20 g; severe: >20 g

Iron Overload: Classification

1. Hereditary conditions causing ↓ hepcidin
   - HFE hemochromatosis
   - TFR2 hemochromatosis
   - Hemojuvelin hemochromatosis
   - Hepcidin hemochromatosis

2. Hereditary conditions causing resistance of ferroportin to hepcidin
   - Ferroportin disease

3. Ineffective erythropoiesis: erythroblast-derived erythroferrone suppresses hepcidin:
   - β-thal major & intermedia; Hb E/β-thal; Hb H
   - congenital dyserythropoietic and sideroblastic anemias

4. Multiple blood transfusions
   - Diamond Blackfan anemia
   - aplastic anemia
   - thalassemia major
   - sickle cell anemia
   - myelodysplasia

5. Other hereditary conditions
   - Aceruloplasminemia
   - Atransferrinemia
   - African dietary iron overload
### Fe Overload: Clinical Manifestations

1. Fatigue, abd. pain
2. Liver
   - ↑ ALT
   - fibrosis and cirrhosis
   - Hepatoma
3. Heart
   - CHF (restrictive or dilated)
   - arrhythmias
4. Endocrine
   - diabetes mellitus
   - secondary amenorrhea
   - Impotence
5. Hyperpigmentation
6. Certain infections
7. Arthritis
   - esp. 1st and 2nd MP joints (HFE hemochromatosis)

### Screening for hemochromatosis or increased iron stores

1. Screen pts
   - with family hx or compatible clinical picture
   - without inflamm., infection, trauma, surgery
2. Serum ferritin conc.
   - ↑ raises possibility (esp. if Tf Sat ↑ or upper nl)
   - Ferritin >1000 ug/L esp. of concern
3. PCR for HFE mutations, esp. Caucasians

### Diagnosis of hemochromatosis or increased iron stores

1. Liver biopsy
   - Histology
   - Perl’s stain
   - Chemical iron concentration
2. MRI measurement hepatic or cardiac iron
3. SQUID magnetic measurement hepatic iron
4. Quantitative phlebotomy

### Liver Bx, HFE hemochromatosis (H&E):

- Golden brown hemosiderin pigment predominantly in hepatocytes

### Liver Bx, HFE hemochromatosis

**Prussian blue stain:**

- Granules predominantly in hepatocytes

**Cirrhosis; hepatocytes in regenerating nodule heavily laden with iron**
**HFE Hemochromatosis**

1. Classic triad
   - Hepatomegaly
   - Diabetes
   - Hyperpigmentation
2. Classically death from cirrhosis, HCC or CHF
3. Goal now—make dx and rx in presymptomatic stage

**HFE Genetic Defect**

1. C282Y mutation, HFE gene, 6p21.3
   - Autosomal recessive
   - Predominantly in N. Europeans: “Celtic Disease”
   - high prevalence in pop.
     - homozygotes: 3-5/1000
     - heterozygotes: 10-15%

2. HFE protein deficiency
   - ↓ hepcidin production
   - ↑ Fe absorption
   - ↑ serum Fe and transferrin saturation
   - ↓ storage of Fe in macrophages
   - Fe-loading of parenchymal cells

**HFE C282Y in 99,711 1º Care Pts (HEIRS)**

<table>
<thead>
<tr>
<th></th>
<th>C282Y/ C282Y</th>
<th>No. per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>44,082</td>
<td>0.44%</td>
</tr>
<tr>
<td>African</td>
<td>27,124</td>
<td>0.014%</td>
</tr>
<tr>
<td>Americans</td>
<td>12,772</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hispanics</td>
<td>12,459</td>
<td>0.027%</td>
</tr>
</tbody>
</table>

**Management of HFE hemochromatosis**

1. NL life expectancy if phlebotomy Rx started before cirrhosis or diabetes
2. If ferritin <1000 μg/L and LFTs nl at dx
   - Proceed to phlebotomy therapy
3. If ferritin >1000 and/or LFTs abnl
   - Consider liver biopsy
   - ↑ risk HCC in cirrhotics even with phleb. Rx
4. Screen first degree family members

**Phlebotomy Therapy**

1. Initial program to remove excess body Fe
   - Remove 1-2 units of blood weekly as long as Hct ≥ 35% (M) or 32% (F).
   - Continue until mild iron deficit: Pt. does not tolerate wkly phleb.; MCV declines; ft < 50 ug/L
Phlebotomy Therapy

2. Quantitative phlebotomy
   • Maintain weekly schedule and tally ml of whole blood removed until Fe deficiency develops.
   • Calculate Fe stores at beginning of program (1 mg Fe/2 ml whole blood); >4g Fe- “Fe overload”

3. Maintenance to prevent the Fe reaccumulation
   • Remove 1 unit each 2-6 mos. to maintain serum fttn around 50 μg/L.

Other Forms of Genetic Hemochromatosis

• Ferroportin disease
  – autosomal dominant mutations ferroportin 2q32
  – two phenotypes
    • reduced response to hepcidin: predominant parenchymal iron-loading
    • increased sensitivity to hepcidin: predominant macrophage iron-loading

African Iron Overload

1. High dietary Fe in traditional beverage
2. Familial pattern
   – ? "gene by environment interaction"
   – HFE mutations not present
   – Ferroportin Q24H in some iron-loaded subjects
3. Fe-loading macrophages and hepatocytes

Iron Overload in African Americans

• Condition present; may be under-dxed
• Sometimes related to African-specific ferroportin Q248H mutation
• Screen with serum ferritin
• Responds well to phlebotomy therapy
• Evaluate for hepatitis C- may play etiologic role by suppressing hepcidin

Other Forms of Genetic Hemochromatosis

• TFR2 hemochromatosis
  – autosomal recessive; intermediate phenotype
  – TFR2 mutation 7q22
• Juvenile hemochromatosis
  – autosomal recessive; severe phenotype
  – hemjuvelin mutation 1q21.1
  – HAMP (hepcidin) mutation 19q13.1

Transfusional Iron Overload

Quantitative Considerations

• One unit blood contains about 225 mg Fe as Hb
• Hepatic Fe concentration
  – normal <30 μmol/g dry wt. 0 units
  – worrisome 180 μmol/g dry wt. 50 units
  – Toxic 360 μmol/g dry wt. 100 units
  – highly toxic 720 μmol/g dry wt. 200 units
• At 2 units/month: 50 units in two yrs
Transfusional Iron Overload Treatment
1. Institute iron chelation when
   - >20 units of blood transfused, or
   - hepatic iron conc. > 180 µmol/g dry wt.
2. Desferrioxamine, original parenteral chelator
   - 40-50 mg/kg per day
   - s.c. infusion over 8-12 hours
   - 5 days/week
3. Deferasirox
   - Single oral dose per day; similar potency to DFO
   - Exjade: powder; starting dose 20 mg/kg/day; advance to 30 or 40 mg/kg/day if needed
   - Jadenu: tablet; doses slightly lower
   - Monitor CBC, creatinine, LFTs, gastritis sx’s q2-4wks
4. Deferiprone
   - Oral chelator
   - Risk of agranulocytosis
   - Approved in US for use in thalassemia patients with transfusional iron overload who did not respond to other chelators

Monitoring Iron Chelation Rx
1. CBC; renal and liver function tests; GI Sxs monthly
2. Audiometry and ophthalmologic yearly
3. Serum ferritin every three months
4. Avoid use of phenothiazines
5. Vitamin C 100 mg daily may enhance Fe excretion; do not give to heavily iron-loaded subjects
6. Modify dose as body Fe burden ↓’s

Other Iron Overload Conditions
1. Congenital atransferrinemia (3q22.1)
   - parenchymal Fe-loading; anemia
2. Congenital aceruloplasminemia (3q23-q25)
   - Fe-loading parenchyma, macrophages, brain
   - extrapyramidal sx's, cerebellar ataxia, DM
3. Neuroferritinopathy
   - autosomal dominant, late-onset
   - abnl aggregates ferritin & Fe in basal ganglia
   - Mut. ftyn light gene (19q13.3-13.4); ser. ftyn low
4. Hallovorden-Spatz disease
   - autosomal recessive; onset in childhood
   - iron deposits in the basal ganglia
   - mutation in pantothenate kinase 2 gene (20p13)