IRON METABOLISM DISORDERS

ANEMIA

Definition

• Decrease in the number of circulating red blood cells

• Most common hematologic disorder by far
ANEMIA

Causes

- Blood loss
- Decreased production of red blood cells (Marrow failure)
- Increased destruction of red blood cells
  - Hemolysis
- Distinguished by reticulocyte count
  - Decreased in states of decreased production
  - Increased in destruction of red blood cells

ANEMIA

Causes - Decreased Production

- Cytoplasmic production of protein
  - Usually normocytic (MCV 80-100 fl) or microcytic (MCV < 80 fl)
- Nuclear division/maturation
  - Usually macrocytic (MCV > 100 fl)
ANEMIA

Causes - Cytoplasmic Protein Production

- Decreased hemoglobin synthesis
  - Disorders of globin synthesis
  - Disorders of heme synthesis
- Heme synthesis
  - Decreased Iron
  - Iron not in utilizable form
  - Decreased heme synthesis

IRON DEFICIENCY ANEMIA

Prevalence

<table>
<thead>
<tr>
<th>Country</th>
<th>Men (%)</th>
<th>Women (%)</th>
<th>Pregnant Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. India</td>
<td>6</td>
<td>35</td>
<td>56</td>
</tr>
<tr>
<td>N. India</td>
<td>64</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>4</td>
<td>17</td>
<td>38</td>
</tr>
<tr>
<td>Israel</td>
<td>14</td>
<td>29</td>
<td>47</td>
</tr>
<tr>
<td>Poland</td>
<td></td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>1</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>
IRON

- Functions as electron transporter; vital for life
- Must be in ferrous (Fe\(^{+2}\)) state for activity
- In anaerobic conditions, easy to maintain ferrous state
- Iron readily donates electrons to oxygen, \(\Rightarrow\) superoxide radicals, \(\text{H}_2\text{O}_2\), \(\text{OH}^-\) radicals
- Ferric (Fe\(^{+3}\)) ions cannot transport electrons or \(\text{O}_2\)
- Organisms able to limit exposure to iron had major survival advantage

**Body Compartments - 75 kg man**

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Stores</th>
<th>Tissue</th>
<th>Red Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg</td>
<td>1000</td>
<td>170</td>
<td>2400</td>
</tr>
</tbody>
</table>

Absorption < 1 mg/day
Excretion < 1 mg/day
IRON

Causes of Iron Deficiency

• Blood Loss
  - Gastrointestinal Tract
  - Menstrual Blood Loss
  - Urinary Blood Loss (Rare)
  - Blood in Sputum (Rarer)
• Increased Iron Utilization
  - Pregnancy
  - Infancy
  - Adolescence
  - Polycythemia Vera
• Malabsorption
  - Tropical Sprue
  - Gastrectomy
  - Chronic atrophic gastritis
• Dietary inadequacy (almost never sole cause)
• Combinations of above

DAILY IRON REQUIREMENTS

Pregnancies
**Iron Absorption**

![Bar chart showing iron absorption](chart.png)

**GI Absorption of Iron**

![Diagram of GI absorption](diagram.png)

*Fig. 3.4 The regulation of iron absorption. The protein DMT1 transports iron across the duodenal microvillus tip of enterocytes at the apex of the villi. Entry of iron from the cell is conducted by ferroportin. The heme/iron-binding protein HFE is expressed at the basolateral surface of enterocytes and binds to the transferrin receptor where it seems to control uptake of iron into the cell from portal blood. In the normal situation, iron is incorporated into crypt cells by ferroportin and transported to the enterocyte, which contains the increased expression of the IRP1 and IRP2 proteins. In hereditary hemochromatosis (HFE) in patients with increased iron absorption (Fig. 3.3), expression of transferrin receptor (TR) increases, so iron levels in erythrocytes are low in relation to body iron stores. DMT1 expression is consequently high and iron absorption increased.*
FERRITIN/TRANSFERRIN REGULATION

Fig. 3.3 Regulation of transferrin receptor (TRR), DMT-1 (divalent metal transporter), ferritin and ferritin expression by iron regulatory protein (IRP) sensing of intracellular iron levels. IRPs are able to bind to stem-loop structures called iron response elements (IREs). IRPs bind to the IRE within the 5' untranslated region of ferritin mRNA, reducing translation. IRPs can exist in two states—a high affinity state at low iron levels and a low affinity state at high iron levels. When IRPs bind to the IRE, ferritin synthesis is increased.

IRON ABSORPTION

Iron absorbed (mg/day) vs. iron ingested (mg/day) graph showing a sigmoidal relationship.

Iron ingested (mg/day) 0.1 1 8 10 20 80 100 200
Iron absorbed (mg/day) 0.01 0.1 1 10 100
IRON DEFICIENCY ANEMIA

Progression of Findings

- Stainable Iron, Bone Marrow Aspirate
- Serum Ferritin - Low in Iron Deficiency
- Desaturation of transferrin
- Serum Iron drops
- Transferrin (Iron Binding Capacity) Increases
- Blood Smear - Microcytic, Hypochromic; Aniso- & Poikilocytosis
- Anemia
Iron Stores
Iron Deficiency Anemia

Stores 0 mg

Tissue 170 mg 3 mg

Absorption 2-10 mg/day
Excretion Dependent on Cause

Red Cells 1500 mg
IRON DEFICIENCY

*Symptoms*

- Fatigue - Sometimes out of proportion to anemia
- Atrophic glossitis
- Pica
- Koilonychia (Nail spooning)
- Esophageal Web

IRON

*Causes of Iron Deficiency*

- Blood Loss
  - Gastrointestinal Tract
  - Menstrual Blood Loss
  - Urinary Blood Loss (Rare)
  - Blood in Sputum (Rarer)
- Increased Iron Utilization
  - Pregnancy
  - Infancy
  - Adolescence
  - Polycythemia Vera
- Malabsorption
  - Tropical Sprue
  - Gastrectomy
  - Chronic atrophic gastritis
- Dietary inadequacy (almost never sole cause)
- Combinations of above
IRON REPLACEMENT THERAPY
Response

• Usually oral; usually 300-900 mg/day
• Requires acid environment for absorption
• Poorly absorbed

IRON THERAPY
Response

• Initial response takes 7-14 days
• Modest reticulocytosis (7-10%)
• Correction of anemia requires 2-3 months
• 6 months of therapy beyond correction of anemia needed to replete stores, assuming no further loss of blood/iron
• Parenteral iron possible, but problematic
Hemochromatosis-1

- Disease of excess iron uptake
- 2% of population has hemochromatosis; inherited as autosomal dominant
- Exists worldwide, but
  - Belt across Northern Europe with increased incidence
    - Ireland, Scandinavia, Russia
- Defects can be in DMT-1, more commonly in HFE (genetic defects only really studied for northern Europeans)
- Can also have acquired hemochromatosis, from transfusion for other illnesses

Hemochromatosis -2

- Defect in HFE causes decreased iron uptake by crypt enterocytes
- Leads to increased DMT-1, causing increased iron extraction from diet & increased iron delivery to tissues
- Once iron is absorbed, very difficult to remove
Hemochromatosis-3

- Sequence of events:
  - Increased ferritin
  - Increased transferrin saturation
    - Normal c. 33%; if > 60%, often marker for disease; if > 90-95%, can start to get free iron
  - Increased iron binding to other transport proteins
    - Albumin
- Iron deposition in tissues, leading to:

Hemochromatosis-4

- Diseases
  - Skin darkening
    - Due to iron deposition in skin causing increased melanin production
  - Endocrinopathy
    - Diabetes, hypothyroidism, hypopituitarism
  - Liver damage
    - Can lead to cirrhosis, hepatocellular CA
  - Cardiac damage
    - Cardiomyopathy leading to congestive heart failure
Hemochromatosis-5

- Treatment
  - Early recognition
  - Phlebotomy
  - Iron chelation – Generally reserved for transfusion-induced hemochromatosis

ANEMIA OF CHRONIC DISEASE

Findings

- Mild, non-progressive anemia (Hgb c. 10, Hct c. 30%)
- Other counts normal
- Normochromic/normocytic (30% hypochromic/microcytic)
- Mild aniso- & poikilocytosis
- Somewhat shortened RBC survival
- Normal reticulocyte count (Inappropriately low for degree of anemia)
- Normal bilirubin
- EPO levels increased but blunted for degree of anemia
ANEMIA OF CHRONIC DISEASE

Causes

- Thyroid disease
- Collagen Vascular Disease
  - Rheumatoid Arthritis
  - Systemic Lupus Erythematosus
  - Polymyositis
  - Polyarteritis Nodosa
- Inflammatory Bowel Disease
  - Ulcerative Colitis
  - Crohn’s Disease
- Malignancy
- Chronic Infectious Diseases
  - Osteomyelitis
  - Tuberculosis
- Familial Mediterranean Fever

IRON STORES

Anemia of Chronic Disease

Stores 2500 mg

Tissue 170 mg

Red Cells 1100 mg

Absorption < 1 mg/day
Excretion < 1 mg/day

1 mg
IRON CYCLE
Anemia of Chronic Disease

CIRCULATING RBCs
MONONUCLEAR PHAGOCYTES

TRANSPORTER RECEPTOR
RBC PRECURSOR
TRANSFERRIN

Fe
Fe
Fe
Fe
Fe

IL-1/TNF

Fe
Fe
Fe
Fe

Ferritin
Hemosiderin
IRON DEFICIENCY *versus* ACD

<table>
<thead>
<tr>
<th>Serum Iron</th>
<th>Transferrin</th>
<th>Ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Soluble Transferrin Receptor

- Measure of ferrokinetic activity
- Elevated in iron deficiency
- Not usually elevated in anemia of chronic inflammation (not an acute phase reactant)
- Still not widely available
- Expensive
- May replace iron binding capacity &/or ferritin
SUMMARY
Iron Metabolism Disorders

• Most common form of anemia
• Symptom of pathologic process
• Primary manifestation is hematologic
• Treatment requires:
  - Replacement therapy
  - Correction of underlying cause (if possible)
• Iron excess more dangerous than iron deficiency