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>
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<td>N. India</td>
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<td>80</td>
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<td>Poland</td>
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<td>Sweden</td>
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<tr>
<td>USA</td>
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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, superoxide radicals, H$_2$O$_2$, OH• radicals
• Ferric (Fe$^{+3}$) ions cannot transport electrons or O$_2$
• Organisms able to limit exposure to iron had major survival advantage
IRON

Body Compartments - 75 kg man

Stores 1000 mg

Tissue 170 mg 4 mg

Red Cells 2400 mg

Absorption < 1 mg/day

Excretion < 1 mg/day
IRON CYCLE

CIRCULATING RBCs

MONONUCLEAR PHAGOCYTES

TRANSFERRIN

RBC PRECURSOR

Ferritin

Hemosiderin

Fe

Fe

Fe

Fe

Fe

Fe

Fe

Fe

Fe

Fe

Fe
INTRACELLULAR IRON TRANSPORT

$Fe^{+2}$

Transferrin

Transferrin receptor

Lysosome

$H^+$

$Fe^{+2}$
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**

<table>
<thead>
<tr>
<th>Age</th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>0</td>
<td>1.4</td>
<td>0.5</td>
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<tr>
<td>2</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>2.3</td>
<td>2.0</td>
</tr>
<tr>
<td>20</td>
<td>2.7</td>
<td>2.5</td>
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<td>30</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>40</td>
<td>3.5</td>
<td>3.5</td>
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</table>

**Pregnancies**

- 2 pregnancies: Males: 2.5 mg/day, Females: 1 mg/day
- 5 pregnancies: Males: 2.0 mg/day, Females: 2 mg/day

The graph shows absorbed iron requirement (mg/day) by age and gender. The requirement increases with age and varies by gender, with females generally requiring more iron than males.
IRON ABSORPTION

Iron (mg/day)

Iron in Diet

Iron Solubilized

Iron Uptake

Iron Absorbed
GI ABSORPTION OF IRON

Fig. 3.4 The regulation of iron absorption. The protein DMT-1 transports iron across the duodenal microvillus brush border at the apex of the villus. Exit of iron from the cell is controlled by ferroportin. The haemochromatosis protein HFE is expressed at the basolateral surface of crypt cells 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 enterocytes from transferrin and the adequate supply of iron leads to physiological levels of DMT-1 and ferroportin expression. In iron deficiency there is reduced delivery of iron to the enterocytes leading to greater expression of DMT-1 and probably of ferroportin (Fig. 3.3) and consequently increased iron absorption and transfer of iron to portal plasma. In hereditary haemochromatosis HFE is mutated, preventing iron incorporation into the crypt enterocytes so iron levels within enterocytes are low in relation to body iron stores. UDV-1 expression is consequently high and iron absorption increased.
Fig. 3.3 Regulation of transferrin receptor (Tfr), DMT-1 (divalent metal transporter), ferroportin 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) (↑) in transferrin receptor or ferritin messenger RNA (∆mRNA∆). IRP binding to the IRE within the 5’ untranslated region of ferritin mRNA reduces translation. IRPs can exist in two states — at times of high iron levels the IRP binds iron and exhibits a reduced affinity for the IREs whereas when iron levels are low the binding of IRPs to IREs is increased. In this way synthesis of Tfr, DMT-1 and ferritin is coordinated to physiological requirements.

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IRON ABSORPTION

Iron Ingested (mg/day)

Iron Absorbed (mg/day)

Iron Absorbed (mg/day) vs. Iron Ingested (mg/day)
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
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  - Menstrual Blood Loss
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• 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 due to allergic reactions
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

- 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

1 mg

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

Red Cells 1100 mg
IRON CYCLE

Anemia of Chronic Disease

CIRCULATING RBCs

MONONUCLEAR PHAGOCYTES

Fe Fe
Ferritin

Fe Fe
Ferritin Transferrin

RBC PRECURSOR

TRANSFERRIN

IL-1/TNF

Hemosiderin

Fe Fe
Fe Fe
Fe Fe

Ferritin Receptor

Fe Fe
Fe Fe
IRON DEFICIENCY versus ACD

<table>
<thead>
<tr>
<th>Serum Iron</th>
<th>Transferrin</th>
<th>Ferritin</th>
</tr>
</thead>
</table>

Iron Deficiency

ACD
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