Anemias of Disordered Iron Metabolism and Heme Synthesis

Iron Metabolism - Distribution
- Iron-containing compounds
  - Functional compounds – metabolic (hemoglobin) or enzymatic functions
  - Transport (transferrin) or storage (ferritin)
- Total iron concentration = 40-50 mg/kg body weight (60-75% in hemoglobin)
- Hemoglobin from degrading RBC is degraded in liver, spleen – iron is released.
- 85% of this iron is recycled – delivered to bone marrow bound to transferrin

Iron Metabolism - Absorption
- Primarily in mucosa of proximal small intestine –
- Amount absorbed depends on
  - Amount of iron ingested
  - Form of ingested iron - ferric iron not easily absorbed
  - Tissue iron stores – inversely related to amount absorbed
  - Condition of mucosal cells in GI tract
  - Hematopoietic activity of bone marrow
  - Intraluminal factors (parasites, toxins, etc)

Iron Metabolism - Transport
- Major iron transport protein is transferrin.
- Each gram of transferrin will bind 1.4 mg of iron.
- Total transferrin present in plasma to bind 253-435 μg of iron/dL of plasma – Total iron-binding capacity (TIBC)
- Serum iron concentration is 70 – 201 μg/dL – 95% is complexed with transferrin
Transferrin is about 1/3 saturated with iron (% saturation = serum iron/TIBC X 100%) 
The reserve iron-binding capacity of transferrin is called the **unsaturated iron-binding capacity** or UIBC (UIBC = TIBC – serum iron) 
Most iron bound to transferrin comes from the breakdown of hemoglobin 
Excess iron deposited in tissues

Iron metabolism - Storage
- Major storage depot is liver 
- Stored as ferritin and hemosiderin 
- Ferritin 
  - primary storage compound for body’s need 
  - Readily released for heme synthesis 
  - Small amounts found in blood – parallels the storage iron in the body

Iron Metabolism - Requirements
- Body iron conserved through reutilization – only about 1 mg lost per day 
- Iron deficiency occurs when negative iron balance 
  - Increased requirements 
  - Inadequate diet 
  - Malabsorption 
- Iron overload when 
  - Increased absorption 
  - Multiple transfusions 
  - Iron injections

Hemosiderin
- Major long term storage form of iron 
- Slow release 
- Estimation of hemosiderin made on bone marrow tissue sections
Increased Iron Requirements

- Menstruation – menstruating females have twice the daily requirements as males (2 mg/day)
- Pregnancy – 3.4 mg/day
- Infancy/childhood – rapid growth
  - At birth, enough iron stores for 4-5 months
  - Milk is poor source of iron
  - Iron supplementation recommended

Laboratory Assessment of Iron

- Serum iron levels
- Total iron binding capacity
- Calculation of % saturation of transferrin
- Serum ferritin

- Ferrokinetic studies (not done routinely) - monitor movement of $^{59}$Fe from plasma to bone marrow and into circulating RBCs.
  - Rate at which iron leaves plasma is PIT (plasma iron turnover) – good indication of total erythropoiesis
  - Rate at which iron incorporated into circulating erythrocytes is EIT (erythrocyte iron turnover) – measure of effective erythropoiesis - correlates with RPI
Iron deficiency Anemia (IDA)

- Most common nutritional deficiency in the world
- Symptoms
  - General anemia symptoms –
    - Shortness of breath on exertion
    - Lethargy
    - Heart palpitations
  - Mucosal atrophy - glossitis, cheilitis, dysphagia
  - "Spoon nails" - koilonychia
  - Pica

Etiology of IDA

- Dietary Deficiency – rarely the cause in developed countries (except in infancy, pregnancy, adolescence)
- Blood Loss –
  - Adult males have about 8 years of storage iron. Deficiency if chronic blood loss – e.g. gastrointestinal or genitourinary bleeding
  - Intravascular hemolysis
- Malabsorption

Etiology vs. Pathophysiology

- Etiology is the cause or origin of a disorder.
- Pathophysiology is the functional alteration in a disease or a defect.

Normal Values

- Iron: 60-170 μg/dl
- TIBC: 240-450 μg/dl
- Transferrin saturation: 20-50%
Pathophysiology of IDA

- Diminished total body iron content, developing in stages over a period of negative iron balance
  - Iron depletion – Stage One
  - Iron deficient erythropoiesis – Stage Two
  - Iron deficiency anemia – Stage Three

Stage One

- Iron storage is exhausted - indicated by decrease in serum ferritin levels
- No anemia – RBC morphology is normal
- May have elevated RDW

Stage Two

- Insufficient iron to insert into protoporphyrin ring to form heme –
- Protoporphyrin accumulates in cell and complexes with zinc to form ZPP
- No anemia, no hypochromia, but slight microcytosis
- RPI may be decreased

Stage Three

- All laboratory tests for iron status become abnormal
- Most significant finding is microcytic, hypochromic anemia
Laboratory findings – Fe deficiency

- Microcytic/hypochromic anemia – microcytosis first
  - MCV = 55-74 fl
  - MCHC = 22:31 %
  - MCH = 14:26 pg
- Hgb < 10 g/dL
- Increased RDW

- RPI < 2.0 (ineffective erythropoiesis)
- Poikilocytosis (target cells, elliptocytes, dacryocytes)
- May be thrombocytosis
- ↓ serum ferritin
- ↓ Serum iron (<30 μg/dL); ↑ TIBC; ↓ % saturation (<16 %)

Therapy

- Treat underlying disorder
- Administer iron and observe response
  - Oral administration of ferrous sulfate
  - Increase of 1 gm/hemoglobin per month
  - Reticulocyte count peaks at about 8 to 10 days (4-10%)

Anemias Caused by Abnormal Iron Metabolism

- Sideroblastic anemias
- Anemia of chronic disease
Sideroblastic anemia

- Characterized by
  - Increase in total body iron
  - Presence of ringed sideroblasts in bone marrow
  - Hypochromic anemia

Classification

- Hereditary form
- Acquired form (more common)
  - Idiopathic – Refractory anemia with ringed sideroblasts (RARS)
  - secondary

Pathophysiology

- Disturbances of enzymes regulating heme synthesis
- Ringed sideroblasts form when nonferritin iron accumulated in the mitochondria that circle the normoblast nucleus

Hereditary Sideroblastic Anemia

- Most common form is sex-linked and due to an abnormal δ-aminolevulinate synthase enzyme (ALAS)
- Decreased heme synthesis due to block in iron utilization –
  - perceived by body as increased need for iron
  - Increased iron absorption results in iron overload
Acquired Sideroblastic Anemia

- RARS (Refractory anemia with ringed sideroblasts) – acquired stem cell disorder
- Secondary
  - Lead poisoning (plumbism)
    - Associated with hyperactivity, low IQ, concentration disorders in children
    - Inhibits cellular enzymes involved in heme synthesis
  - Alcoholism – alcoholics frequently have anemias due to one or more causes
  - Malignancy

Laboratory findings in SA – Peripheral Blood

- Moderate to severe anemia – dimorphic (mild macrocytosis prevalent in RARS and alcoholism)
- Target cells
- Pappenheimer bodies
- Basophilic stippling – coarse basophilic stippling characteristic in lead poisoning
- $\uparrow$ Fe, N to $\downarrow$ TIBC, $\uparrow$ % saturation, $\uparrow$ ferritin

Bone marrow

- Erythroid hyperplasia - megaloblastosis
- Ringed sideroblasts in 50% of normoblasts

Therapy

- Pyroxidine – hereditary form (50% response)
- Folic acid if megaloblastoid features
- Phlebotomy/chelation therapy to remove excess iron
Anemia of Chronic Disease
- Anemia that occurs in patients with chronic infections, chronic inflammatory disorders, or neoplastic disorders not due to bleeding, hemolysis, or marrow involvement (renal, endocrine, or hepatic insufficiencies are excluded)
- Low serum iron, normal iron stores

Pathophysiology
- Impaired marrow response to anemia – cytokines produced as result of immune response inhibit EPO production
- Block in iron release from macrophage
- Shortened erythrocyte survival

Laboratory findings
- Mild anemia (not less than 9 g/dL)
- Normocytic, normochromic (some are normocytic, hypochromic)
- RPI<2
- ↑ Fe (10-70 μg/dL), N to ↓ TIBC (100-300 μg/dL), N to ↓ % saturation (10-25%), N or ↑ ferritin

Hemochromatosis
- Not an anemia – but will be discussed because of abnormal iron studies
- Parenchymal tissue damage from iron overload – excess iron stored in macrophages and hepatocytes, cardiac cells, endocrine cells
Recessive genetic disorder
- Prevalence of 1 in 200-250 persons
- 1:10 Caucasians in US are carriers
- Abnormal protein produced that binds to transferrin receptor on cells –
- Clinical findings
  - Chronic fatigue
  - Diabetes
  - Cirrhosis
  - Hyperpigmentation of skin

Laboratory findings
- Criteria for diagnosis: >50% transferrin saturation in females; >60% in males
- Treatment
  - Phlebotomy – each unit of blood removes about 250 mg of iron

Porphyrias
- Group of inherited disorders characterized by block in porphyrin synthesis
  - Lack of enzyme in pathway of heme synthesis
  - Heme precursors accumulate in tissues – excreted in urine and/or feces
- Symptoms
  - Photosensitivity
  - Abdominal pain
  - Neuropathy
- 2 forms depending on primary site of defective porphyrin metabolism
  - Hepatic
  - Erythropoietic – (we will discuss these because they affect the erythrocytes)
Pathophysiology of EP

- Abnormality of heme biosynthetic pathway within the normoblasts
- 2 types
  - Congenital erythropoietic porphyria (CEP)
  - Erythropoietic protoporphyria (EEP)
- Porphyrinogens are the precursors or porphyrins
  - Series III – precursors of heme
  - Series I - functionless

Congenital Erythropoietic Porphyria

- Excessive amounts of series I porpyrins
- ? Enzyme defect in uropopyringoen III cosynthase so porphyrinogens are channeled to series I isomer
- Excess porpyrins deposited in body tissues –
  - Hemolytic anemia - ? Result of excess porphyrins in RBC

Erythropoietic Protoporphyria

- Overproduction of protoporphyrin
- No anemia present – excess protoporphyrin IX builds up – leaks into skin dermal capillaries

Clinical Features

- CEP – rare autosomal recessive disorder (only ~100 cases reported)
  - Pink to reddish brown urine
  - Excess porphyrins- extreme photosensitivity
  - Vesicular eruptions on skin exposed to sunlight
  - Hypertrichosis
- EEP – autosomal dominant (some autosomal recessive inheritance) – ~300 cases reported
Laboratory Features

- **CEP**
  - Mild to severe N/N anemia with anisocytosis and poikilocytosis
  - Polychromasia with ↑ reticulocytes – RBCs fluoresce with UV light

- **EEP**
  - No abnormalities on routine testing