Iron Deficiency Anemia

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Introduction

Background

Iron deficiency is defined as a decreased total iron body content. Iron deficiency anemia occurs when iron deficiency is sufficiently severe to diminish erythropoiesis and cause the development of anemia. Iron deficiency is the most prevalent single deficiency state on a worldwide basis. It is important economically because it diminishes the capability of individuals who are affected to perform physical labor, and it diminishes both growth and learning in children.

In healthy people, the body concentration of iron (approximately 60 parts per million [ppm]) is regulated carefully by absorptive cells in the proximal small intestine, which alter iron absorption to match body losses of iron (see images below). Persistent errors in iron balance lead to either iron deficiency anemia or hemosiderosis. Both are disorders with potential adverse consequences.
The total body iron in a 70-kg man is about 4 g. This is maintained by a balance between absorption and body losses. Although the body only absorbs 1 mg daily to maintain equilibrium, the internal requirement for iron is greater (20-25 mg). An erythrocyte has a lifespan of 120 days so that 0.8% of red blood cells are destroyed and replaced each day. A man with 5 L of blood volume has 2.5 g of iron incorporated into the hemoglobin, with a daily turnover of 20 mg for hemoglobin synthesis and degradation and another 5 mg for other requirements. Most of this iron passes through the plasma for reutilization. Iron in excess of these requirements is deposited in body stores as ferritin or hemosiderin.
Mucosal cells in the proximal small intestine mediate iron absorption. Intestinal cells are born in the crypts of Lieberkuhn and migrate to the tips of the villi. The cells are sloughed into the intestinal lumen at the end of their 2- to 3-day lifespan. Absorptive cells remain attuned to the body requirement for iron by incorporating proportionate quantities of body iron into the absorptive cells. This iron and recently absorbed iron decrease uptake of iron from the gut lumen by satiation of iron-binding proteins with iron, by stimulating an iron regulatory element, or
both. The incorporation of iron into these cells in quantities proportional to body stores of iron also provides a limited method of increasing iron excretion in individuals replete in iron.

Posthemorrhagic anemia is discussed in this section because it is an important cause of iron deficiency. The acute and potentially catastrophic problems of hypoxia and shock that can occur from significant hemorrhage or severe iron deficiency are discussed elsewhere in the textbook; however, daily blood losses can be small and may be overlooked. Occasionally, patients with severe iron deficiency anemia from slow but persistent gastrointestinal bleeding have repeatedly negative testing of stool for hemoglobin. Therefore, it is important for the clinician to be aware of characteristics of the anemia at all intervals after the onset of bleeding.

Pathophysiology

Iron is vital for all living organisms because it is essential for multiple metabolic processes, including oxygen transport, DNA synthesis, and electron transport. Iron equilibrium in the body is regulated carefully to ensure that sufficient iron is absorbed in order to compensate for body losses of iron.

While body loss of iron quantitatively is as important as absorption in terms of maintaining iron equilibrium, it is a more passive process than absorption. Consistent errors in maintaining this equilibrium lead to either iron deficiency or iron overload.

Iron balance is achieved largely by regulation of iron absorption in the proximal small intestine. Either diminished absorbable dietary iron or excessive loss of body iron can cause iron deficiency. Diminished absorption usually is due to an insufficient intake of dietary iron in an absorbable form.

Hemorrhage is the most common cause of excessive loss of body iron, but it can occur with hemoglobinuria from intravascular hemolysis. Malabsorption of iron is relatively uncommon in the absence of small bowel disease (sprue, celiac disease, regional enteritis) or previous gastrointestinal surgery.

Iron uptake in the proximal small bowel occurs by 3 separate pathways (see image below). These are the heme pathway and separate pathways for ferric and ferrous iron.
Three pathways exist in enterocytes for uptake of food iron. In the United States and Europe, most absorbed iron is derived from heme. Heme is digested enzymatically free of globin and enters the enterocyte as a metalloporphyrin. Within the cell iron is released from heme by heme oxygenase to pass into the body as inorganic iron. Most dietary inorganic iron is ferric iron. This can enter the absorptive cell via the integrin-mobilferrin pathway (IMP). Some dietary iron is reduced in the gut lumen and enters the absorptive cell via the DCT-1 pathway (divalent cation transporter, Nramp-2). The proteins of both pathways interact within the enterocyte with paraferritin, a large protein complex capable of ferrireduction. Excess iron is stored as ferritin to protect the cell from oxidative damage. Iron leaves the cell to enter plasma facilitated by ferroportin and hephaestin, which associate with an apotransferrin receptor. The enterocyte is informed of body requirements for iron by transporting iron from plasma into the cell using a holotransferrin receptor.

In North America and Europe, one third of dietary iron is heme iron, but two thirds of body iron is derived from dietary myoglobin and hemoglobin. Heme iron is not chelated and precipitated by numerous constituents of the diet that renders nonheme iron nonabsorbable (see image below). Examples are phytates, phosphates, tannates, oxalates, and carbonates. Heme is maintained soluble and available for absorption by
globin degradation products produced by pancreatic enzymes. Heme iron and nonheme iron are absorbed into the enterocyte noncompetitively.

Dietary iron contains both heme and nonheme iron. Both chemical forms are absorbed noncompetitively into duodenal and jejunal mucosal cells. Many of the factors that alter the absorption of nonheme iron have little effect upon the absorption of heme iron because of the differences in their chemical structures. Iron is released from heme within the intestinal absorptive cell by heme oxygenase and then transferred into the body as nonheme iron. Factors affecting various stages of iron absorption are shown in this diagram. The simplest model of iron absorption must consider intraluminal, mucosal, and corporeal factors.

Heme enters the cell as an intact metalloporphyrin, presumably by a vesicular mechanism. Heme is degraded within the enterocyte by heme oxygenase with release of iron so that it traverses the basolateral cell membrane in competition with nonheme iron to bind transferrin in the plasma.

Ferric iron utilizes a different pathway to enter cells than ferrous iron. This was shown by competitive inhibition studies, the use of blocking antibodies against divalent metal transporter-1 (DMT-1) and beta3-integrin, and transfection experiments using DMT-1 DNA. This indicated that ferric iron utilizes beta3-integrin and mobilferrin, while ferrous iron uses DMT-1 to enter cells.
Which pathway transports most nonheme iron in humans is not known. Most nonheme dietary iron is ferric iron. Iron absorption in mice and rats may involve more ferrous iron because they excrete moderate quantities of ascorbate in intestinal secretions. Contrariwise, humans are a scorbutic species and are unable to synthesize ascorbate to reduce ferric iron.

Other proteins are described that appear related to iron absorption. These are stimulators of iron transport (SFT), which are reported to increase the absorption of both ferric and ferrous iron, and hephaestin, which is postulated to be important in the transfer of iron from enterocytes into the plasma. The relationship and interactions between the newly described proteins is not known at this time and is being explored in a number of laboratories.

The iron concentration within enterocytes varies directly with the body's requirement for iron. Absorptive cells in iron-deficient humans and animals contain little stainable iron, whereas this is increased significantly in subjects who are replete in iron. Untreated phenotypic hemochromatosis creates little stainable iron in the enterocyte, similar to iron deficiency. Iron within the enterocyte may operate by up-regulation of a receptor, saturation of an iron-binding protein, or both. In contrast to findings in iron deficiency, enhanced erythropoiesis, or hypoxia, endotoxin rapidly diminishes iron absorption without altering enterocyte iron concentration. This suggests that endotoxin and, perhaps, cytokines alter iron absorption by a different mechanism.

Most iron delivered to nonintestinal cells is bound to transferrin. Transferrin iron is delivered into nonintestinal cells via 2 pathways, the classical transferrin receptor pathway (high affinity, low capacity) and the pathway independent of the transferrin receptor (low affinity, high capacity). Otherwise, the nonsaturability of transferrin binding to cells cannot be explained.

In the classical transferrin pathway, the transferrin iron complex enters the cell within an endosome. Acidification of the endosome releases the iron from transferrin so that it can enter the cell. The apotransferrin is delivered by the endosome to the plasma for reutilization. The method by which the transferrin receptor–independent pathway delivers iron to the cell is not known.

Nonintestinal cells also possess the mobilferrin integrin and DMT-1 pathways. Their function in the absence of an iron-saturated transferrin is uncertain; however, their presence in nonintestinal cells suggests they may participate in intracellular functions in addition to their capability to facilitate cellular uptake of iron.

**Frequency**

**United States**

In North America and Europe, iron deficiency is most common in women of childbearing age and as a manifestation of hemorrhage. Iron deficiency caused solely by diet is uncommon in adults in countries where meat is an important part of the diet. Depending upon the criteria used for the diagnosis of iron deficiency, approximately 4-8% of premenopausal women are iron deficient. In men and postmenopausal women, iron deficiency is uncommon in the absence of bleeding.
International

In countries where little meat is in the diet, iron deficiency anemia is 6-8 times more prevalent than in North America and Europe. This occurs despite consumption of a diet that contains an equivalent amount of total dietary iron because heme iron is absorbed better from the diet than nonheme iron. In certain geographic areas, intestinal parasites, particularly hookworm, worsen the iron deficiency because of blood loss from the gastrointestinal tract. Anemia is more profound among children and premenopausal women in these environs.

Mortality/Morbidity

Chronic iron deficiency anemia is seldom a direct cause of death; however, moderate or severe iron deficiency anemia can produce sufficient hypoxia to aggravate underlying pulmonary and cardiovascular disorders.

- Hypoxic deaths have been observed in patients who refuse blood transfusions for religious reasons. Obviously, with brisk hemorrhage, patients may die from hypoxia due to posthemorrhagic anemia.
- While a number of symptoms, such as ice chewing and leg cramps, occur with iron deficiency, the major debility of moderately severe iron deficiency is fatigue and muscular dysfunction that impairs muscular work performance.
- In children, the growth rate may be slowed, and a decreased capability to learn is reported. In young children, severe iron deficiency anemia is associated with a lower IQ, a diminished capability to learn, and a suboptimal growth rate.

Race

Race probably has no significant effect upon the occurrence of iron deficiency anemia; however, because diet and socioeconomic factors play a role in the prevalence of iron deficiency, it more frequently is observed in people of various racial backgrounds living in poorer areas of the world.

Sex

An adult male absorbs and loses about 1 mg of iron from a diet containing 10-20 mg daily. During childbearing years, an adult female loses an average of 2 mg of iron daily and must absorb a similar quantity of iron in order to maintain equilibrium. Because the average woman eats less than the average man does, she must be more than twice as efficient in absorbing dietary iron in order to maintain equilibrium and avoid developing iron deficiency anemia.

- Healthy males lose body iron in sloughed epithelium, in secretions from the skin and gut lining, and from small daily losses of blood from the gastrointestinal tract (0.7 mL of blood daily). Cumulatively, this amounts to 1 mg of iron. Males with severe siderosis from blood transfusions can lose a maximum of 4 mg daily via these routes without additional blood loss.
- A woman loses about 500 mg of iron with each pregnancy. Menstrual losses are highly variable, ranging from 10-250 mL (4-100 mg of iron) per period. These iron losses in women double their need to absorb iron in comparison to males.
Age

Healthy newborn infants have a total body iron of 250 mg (80 ppm), which is obtained from maternal sources. This decreases to approximately 60 ppm in the first 6 months of life, while the baby consumes an iron-deficient milk diet. Infants consuming cow milk have a greater incidence of iron deficiency because bovine milk has a higher concentration of calcium, which competes with iron for absorption. Subsequently, growing children must obtain approximately 0.5 mg more iron daily than is lost in order to maintain a normal body concentration of 60 ppm.

- During adult life, equilibrium between body loss and gain is maintained. Children are more likely to develop iron deficiency anemia. In certain geographic areas, hookworm adds to the problem. Children are more likely to walk in soil without shoes and develop heavy infestations.
- During childbearing years, women have a high incidence of iron deficiency anemia because of iron losses sustained with pregnancies and menses.
- Gastrointestinal neoplasms become increasingly more prevalent with each decade of life. They frequently present with gastrointestinal bleeding that may remain occult for long intervals before it is detected. Usually, bleeding from neoplasms in other organs is not occult, prompting the patient to seek medical attention before developing severe iron depletion.

Clinical

History

While iron deficiency anemia is a laboratory diagnosis, a carefully obtained history can lead to its recognition. The history can be useful in establishing the etiology of the anemia and, perhaps, in estimating its duration.

- Diet
  - A dietary history is important. Vegetarians are more likely to develop iron deficiency, unless their diet is supplemented with iron. National programs of dietary iron supplementation are initiated in many portions of the world where meat is sparse in the diet and iron deficiency anemia is prevalent. Unfortunately, affluent nations also supplement iron in foodstuffs and vitamins without recognizing the potential contribution of iron to free radical formation and the prevalence of genetic iron overloading disorders.
  - Elderly patients, because of poor economic circumstances, may try to survive on a “tea and toast” diet because they do not wish to seek aid. They may also be hesitant to share this dietary information.
  - Pica can be the etiology of iron deficiency among people who habitually eat either clay or laundry starch. Hippocrates recognized clay eating; however, physicians do not recognize it unless the patient and family are specifically queried. Both substances decrease the absorption of dietary iron. Clay eating occurs worldwide in all races, though it is more common in Asia Minor. Starch eating is a habit in females of African
heritage, and it often is started in pregnancy as a treatment for morning sickness.

- **Hemorrhage**
  - Two thirds of body iron is present in circulating red blood cells as hemoglobin. Each gram of hemoglobin contains 3.47 mg of iron; thus, each mL of blood lost from the body (hemoglobin 15 g/dL) results in a loss of 0.5 mg of iron. Bleeding is the most common cause of iron deficiency in North America and Europe. Patients report a history of bleeding from most orifices (hematuria, hematemesis, hemoptysis) before they develop chronic iron deficiency anemia; however, gastrointestinal bleeding may go unrecognized, and excessive menstrual losses may be overlooked.
  - Patients often do not understand the significance of a melanotic stool. Unless menstrual flow changes, patients do not seek medical attention. If they do, they report that their menses are normal in response to inquiry for self-evaluation. Because of the marked differences among women with regard to menstrual blood loss (10-250 mL per menses), query the patient about a specific history of clots, cramps, and the use of multiple tampons and pads.

- **Duration**
  - Iron deficiency in the absence of anemia is asymptomatic. One half of patients with moderate iron deficiency anemia develop pagophagia. Usually, they crave ice to suck or chew. Occasionally, patients are seen who prefer cold celery or other cold vegetables in lieu of ice. Leg cramps, which occur on climbing stairs, also are common in patients deficient in iron.
  - Often, patients can provide a distinct point in time when these symptoms first occurred, providing an estimate of the duration of the iron deficiency.

- **Symptoms**
  - Fatigue and diminished capability to perform hard labor are attributed to the lack of circulating hemoglobin; however, they occur out of proportion to the degree of anemia and probably are due to a depletion of proteins that require iron as a part of their structure.
  - Increasing evidence suggests that deficiency or dysfunction of nonhemoglobin proteins has deleterious effects. These include muscle dysfunction, pagophagia, dysphagia with esophageal webbing, poor scholastic performance, altered resistance to infection, and altered behavior.

**Physical**

- **Anemia produces nonspecific pallor of the mucous membranes.**
- A number of abnormalities of epithelial tissues are described in association with iron deficiency anemia.
  - These include esophageal webbing, koilonychia, glossitis, angular stomatitis, and gastric atrophy.
  - The exact relationship of these findings to iron deficiency is unclear and may involve other factors. For example, in publications from the United Kingdom, esophageal webbing and atrophic changes of the tongue and
the corner of the mouth are reported in as many as 15% of patients with iron deficiency; however, they are much less common in the United States and other portions of the world.

- Splenomegaly may occur with severe, persistent, untreated iron deficiency anemia. This is uncommon in the United States and Europe.

Causes

- Diet
  - Meat provides a source of heme iron, which is less affected by the dietary constituents that markedly diminish bioavailability than nonheme iron is. The prevalence of iron deficiency anemia is low in geographic areas where meat is an important constituent of the diet. In areas where meat is sparse, iron deficiency is commonplace.
  - Substances that diminish the absorption of ferrous and ferric iron are phytates, oxalates, phosphates, carbonates, and tannates (see image below). These substances have little effect upon the absorption of heme iron. Similarly, ascorbic acid increases the absorption of ferric and ferrous iron and has little effect upon the absorption of heme iron.

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**Inorganic Iron**

**Heme**

Both nonheme iron and heme iron have 6 coordinating bonds; however, 4 of the bonds in heme bind pyrroles, making them unavailable for chelation by other compounds. Therefore, ascorbic acid chelates nonheme iron to enhance absorption but has no effect upon heme iron. Many dietary components, such as phytates, phosphates, oxalates, and tannates, bind nonheme iron to decrease nonheme iron absorption. They do not affect heme. This explains why heme is so effectively absorbed with foods containing these chelators. Iron hemoglobin structure.
Purified heme is absorbed poorly because heme polymerizes into macromolecules. Globin degradation products diminish heme polymerization, making it more available for absorption. They also increase the absorption of nonheme iron because the peptides from degraded globin bind the iron to prevent both precipitation and polymerization; thus, absorption of iron in spinach is increased when eaten with meat. Heme and nonheme iron uptake by intestinal absorptive cells is noncompetitive.

Hemorrhage

Bleeding for any reason produces iron depletion. If sufficient blood loss occurs, iron deficiency anemia ensues (see image below). A single sudden loss of blood produces a posthemorrhagic anemia that is normocytic. The bone marrow is stimulated to increase production of hemoglobin, thereby depleting iron in body stores. Once they are depleted, hemoglobin synthesis is impaired and microcytic hypochromic erythrocytes are produced.
Sequential changes in laboratory values following blood loss are depicted. A healthy human was bled 5 L in 500-mL increments over 45 days. A moderate anemia ensued, initially with normal cellular indices and serum iron. Subsequently, the mean corpuscular volume (MCV) increased as iron was mobilized from body stores and reticulocytosis occurred. The serum iron decreased, followed by an increase in the total iron-binding capacity. Gradual decreases in the red blood cell indices occurred, with maximal microcytosis and
hypochromia present 120 days after bleeding. Values returned to normal approximately 250 days after blood loss. At the end of the experiment, iron was absent from body stores (marrow) because hemoglobin has a first priority for iron. Iron-59 absorption was increased after all values returned to normal in order to replenish the body store with iron. This suggests that the serum iron, total iron-binding capacity, hemoglobin concentration, and indices were not the primary regulators of iron absorption.

- Maximal changes in the red blood cell cellular indices occur in approximately 120 days, at a time when all normal erythrocytes produced prior to the hemorrhage are replaced by microcytes. Prior to this time, the peripheral smear shows a dimorphic population of erythrocytes, normocytic cells produced prior to the bleed, and microcytic cells produced after bleeding. This is reflected in the red blood cell distribution width (RDW); thus, the earliest evidence of the development of an iron-deficient erythropoiesis is seen in the peripheral smear and by an increased RDW.

- Hemosiderinuria, hemoglobinuria, and pulmonary hemosiderosis
  - Iron deficiency anemia can occur from loss of body iron in the urine. If a freshly obtained urine specimen appears bloody but contains no red blood cells, suspect hemoglobinuria. Obtain confirmation in the laboratory that the pigment is hemoglobin and not myoglobin. This can be accomplished easily because 60% ammonium sulfate precipitates hemoglobin but not myoglobin.
  - Hemoglobinuria classically is ascribed to paroxysmal nocturnal hemoglobinuria, but it can occur with any brisk intravascular hemolytic anemia. In the early days of heart surgery with implantation of artificial valves, this mechanism of producing iron deficiency anemia was commonplace in large university hospitals. Today, with better prostheses, it has become a less frequent clinical problem. With less severe hemolytic disorders, there may be no significant hemoglobinuria. Investigate renal loss of iron by staining the urine sediment for iron. Hemosiderin is detected intracellularly. Most of these patients have a low or absent plasma haptoglobin. Similarly, pulmonary hemosiderosis can result in sufficient loss of iron as hemosiderin from the lungs.

- Malabsorption of iron
  - Prolonged achlorhydria may produce iron deficiency because acidic conditions are required to release ferric iron from food. Then, it can be chelated with mucins and other substances (amino acids, sugars, amino acids, amides) to keep it soluble and available for absorption in the more alkaline duodenum.
  - Starch and clay eating produce malabsorption of iron and iron deficiency anemia. Specific inquiry is required to elicit a history of either starch or clay eating because patients do not volunteer the information.
  - Extensive surgical removal of the proximal small bowel or chronic diseases, such as untreated sprue or celiac syndrome, can diminish iron
absorption. Rarely, patients with no history of malabsorption have iron deficiency anemia and fail to respond to oral iron therapy. Most merely are noncompliant with therapy. Before placing these patients on parenteral therapy, document iron malabsorption by either measuring absorption of radioiron or by obtaining a baseline fasting serum-iron concentration and repeating the test one-half hour and 1 hour after administration of a freshly prepared oral solution of ferrous sulfate (50-60 mg of iron) under observation. The serum iron should increase by 50% over the fasting specimen.

- Genetic abnormalities producing iron deficiency have been shown in rodents (sex-linked anemia [sla] mice, microcytic anemia [mk] mice, Belgrade rat). This has not been clearly demonstrated in humans, and if it exists, it is probably an uncommon cause of iron deficiency anemia.

**Differential Diagnoses**

Spherocytosis, Hereditary
Thalassemia, Alpha
Thalassemia, Beta

**Other Problems to Be Considered**

Anemia of chronic disorders
Hemoglobin CC disease
Hemoglobin DD disease
Lead poisoning
Microcytic anemias
Sideroblastic anemias

**Workup**

**Laboratory Studies**

- CBC count
  - This documents the severity of the anemia. In chronic iron deficiency anemia, the cellular indices show a microcytic and hypochromic erythropoiesis, ie, both the mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) have values below the normal range for the laboratory performing the test. Reference range values for the MCV and MCHC are 83-97 fL and 32-36 g/dL, respectively.
  - Often, the platelet count is elevated (>450,000/µL). This normalizes following iron therapy.
  - The WBC count is usually within reference ranges (4500-11,000/µL).
  - If the CBC count is obtained after blood loss, the cellular indices do not enter the abnormal range until most of the erythrocytes produced before the bleed are destroyed at the end of their normal lifespan (120 d).

- Peripheral smear
Examination of the peripheral smear is an important part of the workup of patients with anemia. Examination of the erythrocytes shows microcytic and hypochromic red blood cells in chronic iron deficiency anemia. The microcytosis is apparent in the smear long before the MCV is decreased after an event producing iron deficiency. Platelets usually are increased in this disorder.

Unlike thalassemia, target cells usually are not present, and anisocytosis and poikilocytosis are not marked. It lacks the intraerythrocytic crystals seen in hemoglobin C disorders.

Combined folate deficiency and iron deficiency are commonplace in areas of the world with little fresh produce and meat. The peripheral smear reveals a population of macrocytes mixed among the microcytic hypochromic cells. This combination can normalize the MCV.

Serum iron, total iron-binding capacity (TIBC), and serum ferritin: A low serum iron and ferritin with an elevated TIBC are diagnostically of iron deficiency. While a low serum ferritin is virtually diagnostic of iron deficiency, a normal serum ferritin can be seen in patients who are deficient in iron and have coexistent diseases (hepatitis, anemia of chronic disorders). These test findings are useful in distinguishing iron deficiency anemia from other microcytic anemias (see image below).
The sequence of events (left to right) that occur with gradual depletion of body stores of iron. Serum ferritin and stainable iron in tissue stores are the most sensitive laboratory indicators of mild iron deficiency and are particularly useful in differentiating iron deficiency from the anemia of chronic disorders. The percentage saturation of transferrin with iron and free erythrocyte protoporphyrin values do not become abnormal until tissue stores are depleted of iron. Subsequently, a decrease in the hemoglobin concentration occurs because iron is unavailable for heme synthesis. Red blood cell indices do not become abnormal for several months after tissue stores are depleted of iron.

- A bone marrow aspirate can be diagnostic of iron deficiency. The absence of stainable iron in a bone marrow aspirate that contains spicules and a simultaneous control specimen containing stainable iron permit establishment of a diagnosis of iron deficiency without other laboratory tests.
- Other laboratory tests are useful to establish the etiology of iron deficiency anemia and to exclude or establish a diagnosis of 1 of the other microcytic anemias.
  - Testing stool for the presence of hemoglobin is useful in establishing gastrointestinal bleeding as the etiology of iron deficiency anemia. Usually, chemical testing that detects more than 20 mL of blood loss daily from the upper gastrointestinal tract is employed. More sensitive tests are available; however, they produce a high incidence of false-positive results in people who eat meat. Severe iron deficiency anemia can occur in patients with a persistent loss of less than 20 mL/d.
  - To detect blood loss, the patient can be placed on a strict vegetarian diet for 3-5 days and the stool can be tested for hemoglobin using a benzidine method, or red blood cells can be radiolabeled with radiochromium and retransfused. Stools are collected, and the radioactivity is quantified in a gamma-detector and compared to the radioactivity in a measured quantity of the patient's blood. An immunological method of detecting human species-specific hemoglobin in stool is under development and could increase specificity and sensitivity.
- Hemoglobinuria and hemosiderinuria can be detected by laboratory testing as described under Causes. This documents iron deficiency to be due to renal loss of iron and incriminates intravascular hemolysis as the etiology.
- Hemoglobin electrophoresis and measurement of hemoglobin A₂ and fetal hemoglobin are useful in establishing either beta-thalassemia or hemoglobin C or D as the etiology of the microcytic anemia. Unfortunately, simple tests do not exist for alpha-thalassemia in most laboratories, and it is a diagnosis of exclusion.
- Reticulocyte hemoglobin content (CHr) - Mateos Gonzales et al assessed the diagnostic efficiency of commonly used hematologic and biochemical markers, as well as the CHr in the diagnosis of iron deficiency in children, with or without anemia. The investigators identified CHr and iron serum as the only parameters that were independently associated with iron deficiency (P <0.05), and CHr was the strongest predictor of iron deficiency and iron deficiency
anemia. Mateos Gonzalez et al concluded that measurement of CHr may be a reliable method to assess deficiencies in tissue iron supply and, in combination with a CBC count, may be an alternative to the traditional biochemical panel for the diagnosis of iron deficiency in children.\textsuperscript{[1]}

Other Tests

- Incubated osmotic fragility is useful. Microspherocytosis may produce a low-normal or slightly abnormal MCV; however, the MCHC usually is elevated rather than decreased, and the peripheral smear shows a lack of central pallor rather than hypochromia.
- Measure tissue lead concentrations. Chronic lead poisoning may produce a mild microcytosis. The anemia probably is related to the anemia of chronic disorders. The incidence of lead poisoning is greater in individuals who are iron deficient than in healthy subjects because increased absorption of lead occurs in individuals who are iron deficient. Paint in old houses has been a source of lead poisoning in children and painters.

Procedures

A bone marrow aspirate stained for iron (Perls stain) can be diagnostic of iron deficiency provided spicules are present in the smear and a control specimen containing iron is performed at the same time. While this largely has been displaced in the diagnosis of iron deficiency by performance of serum iron, TIBC, and serum ferritin, the absence of stainable iron in a bone marrow aspirate is the criterion standard for the diagnosis of iron deficiency. It is diagnostic in identifying the sideroblastic anemias by showing ringed sideroblasts in the aspirate stained with Perls stain. Occasionally, it is useful in separating patients with the anemia of chronic disorders or alpha-thalassemia from patients with iron deficiency, and it is useful in identifying patients with both iron deficiency and the anemia of chronic disorders.

Histologic Findings

The absence of stainable iron in body tissues, including the bone marrow and liver, is the most useful histological finding in individuals who are iron deficient. Nonspecific abnormalities of epithelial tissues are reported in iron deficiency. These include gastric atrophy and clubbing of the small intestinal villi. While they suggest that iron deficiency is a pantropic disorder, they have little clinical diagnostic value.

Treatment

Medical Care

Medical care consists of establishing the diagnosis and reason for the iron deficiency. In most patients, the iron deficiency should be treated with oral iron therapy, and the underlying etiology should be corrected so the deficiency does not recur.

Surgical Care
Surgical treatment consists of stopping hemorrhage and correcting the underlying defect so that it does not recur. This may involve surgery for treatment of either neoplastic or nonneoplastic disease of the gastrointestinal tract, the genitourinary tract, the uterus, and the lungs.

**Consultations**

- Surgical consultation often is needed for the control of hemorrhage and treatment of the underlying disorder. In the investigation of a source of bleeding, consultation with certain medical specialties may be useful to identify the source of bleeding and to provide control.
- Gastroenterology consultation is the most frequently sought consult among the medical specialties. Endoscopy has become a highly effective tool in identifying and controlling gastrointestinal bleeding. If bleeding is brisk, angiographic techniques may be useful in identifying the bleeding site and controlling the hemorrhage. Radioactive technetium labeling of autologous erythrocytes also is used to identify the site of bleeding. Unfortunately, these radiographic techniques do not detect bleeding at rates less than 1 mL/min and may miss lesions with intermittent bleeding.

**Diet**

- On a worldwide basis, diet is the major cause of iron deficiency. To suggest that iron-deficient populations correct the problem by the addition of significant quantities of meat to their diet is unrealistic. The addition of nonheme iron to national diets is initiated in some areas of the world. Problems encountered in these enterprises include changes in taste and appearance of food after the addition of iron and the need to supplement foodstuffs that are consumed by most of the population in predictable quantities. In addition, many dietary staples, such as bread, contain iron chelators that markedly diminish the absorption of the iron supplement (phosphates, phytates, carbonates, oxalates, tannates).
- In North America and Europe, persons on an iron-poor diet need to be identified and counseled on an individual basis. Educate older individuals on a tea and toast diet about the importance of improving their diet, and place them in contact with community agencies that will provide them with at least 1 nutritious meal daily. Patients who have dietary-related iron deficiency due to pica need to be identified and counseled to stop their consumption of clay and laundry starch.

**Activity**

Restriction of activity is usually not required.

- Patients with moderately severe iron deficiency anemia and significant cardiopulmonary disease should limit their activities until the anemia is corrected with iron therapy.
  - If these patients become hypoxic or develop evidence of coronary insufficiency, they should be hospitalized and placed at bed rest until improvement of their anemia cells can be accomplished by transfusion of packed red blood.
- Obviously, these decisions need to be made on an individual basis and
differ somewhat depending upon the severity of the anemia and the
comorbid conditions.
- March hemoglobinuria can produce iron deficiency, and its treatment requires
modification of activity. Cessation of jogging or wearing sneakers while running
usually diminishes the hemoglobinuria.

**Medication**

The most economical and effective medication in the treatment of iron deficiency
anemia is the oral administration of ferrous iron salts. Among the various iron salts,
ferrous sulfate most commonly is used. Claims are made that other iron salts are
absorbed better and have less morbidity. Generally, the toxicity is proportional to the
amount of iron available for absorption. If the quantity of iron in the test dose is
decreased, the percentage of the test dose absorbed is increased, but the quantity of iron
absorbed is diminished. There are advocates for the use of carbonyl iron because of the
greater safety with children who ingest their mothers' medication. Decreased gastric
toxicity is claimed but not clearly demonstrated in human trials. Bioavailability is
approximately 70% of a similar dose of ferrous sulfate.

Reserve parenteral iron for patients who are either unable to absorb oral iron or who
have increasing anemia despite adequate doses of oral iron. It is expensive and has
greater morbidity than oral preparations of iron.

Reserve transfusion of packed RBC for patients with either significant acute bleeding or
patients in danger of hypoxia and/or coronary insufficiency.

**Mineral supplementations**

These agents are used to provide adequate iron for hemoglobin synthesis and to
replenish body stores of iron. Iron is administered prophylactically during pregnancy
because of anticipated requirements of the fetus and losses that occur during delivery.

**Ferrous sulfate (Feratab, Fer-Iron, Slow-FE)**

Mainstay treatment for treating patients with iron deficiency anemia. They should be
continued for about 2 mo after correction of the anemia and its etiological cause in order
to replenish body stores of iron. Ferrous sulfate is the most common and cheapest form
of iron utilized. Tablets contain 50-60 mg of iron salt. Other ferrous salts are used and
may cause less intestinal discomfort because they contain a smaller dose of iron (25-50
mg). Oral solutions of ferrous iron salts are available for use in pediatric populations.

**Dosing**

**Adult**

325 mg (60 mg iron) PO with each meal tid
Pediatric

Administer weight-based dosing; 3-6 mg/kg/d PO divided tid suggested, depending on severity of anemia

Interactions

Calcium supplementation decreases bioavailability of iron when metals are ingested simultaneously; absorption is enhanced by ascorbic acid; interferes with tetracycline absorption; food and antacids impair absorption

Contraindications

Documented hypersensitivity; microcytic anemias without laboratory documentation of iron deficiency

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Iron poisoning is common in children; preferably, provide tablets containing <20 mg of iron to pregnant women without iron deficiency; adequate as dietary supplement to prevent iron deficiency and reduces risk if child ingests tablets; iron tablets should be dispensed in child-proof containers and stored away from young children; iron pills resemble a commonly available candy; children watch their mother consume iron tablets and then mimic her actions; children who consume multiple iron tablets should be taken to an ED immediately to prevent shock and death; in pregnant women with iron deficiency anemia, pregnancy vitamin and mineral tablets may not suffice to correct deficiency state; administer iron orally separate from the combination tablets

Carbonyl iron (Feosol)

Used as a substitute for ferrous sulfate. Has a slower release of iron and is more expensive than ferrous sulfate. Slower release affords the agent greater safety if ingested by children. On an mg basis, it is 70% as efficacious as ferrous sulfate. Claims are made that there is less gastrointestinal toxicity, prompting use when ferrous salts are producing intestinal symptoms and in patients with peptic ulcers and gastritis. Tablets are available containing 45 mg and 60 mg of iron.

Dosing

Adult

1 tab PO tid (usual dose recommended)
Pediatric

Administer weight-based dosing; 3-6 mg/kg/d PO divided tid suggested, depending on severity of anemia

Interactions

Calcium supplementation decreases bioavailability of iron when metals are ingested simultaneously

Contraindications

Documented hypersensitivity; microcytic anemias without laboratory documentation of iron deficiency

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Iron poisoning is common in children; preferably, provide tablets containing <20 mg of iron to pregnant women without iron deficiency; this is adequate as a dietary supplement to prevent iron deficiency and reduces risk if a child ingests tablets; iron tablets should be dispensed in child-proof containers and stored away from young children; iron pills resemble a commonly available candy; children watch their mother consume iron tablets and then mimic her actions; children who consume multiple iron tablets should be taken to an ED immediately to prevent shock and death

Dextran-iron (INFeD)

Replenishes depleted iron stores in the bone marrow where it is incorporated into hemoglobin. Parenteral use of iron-carbohydrate complexes has caused anaphylactic reactions, and its use should be restricted to patients with an established diagnosis of iron deficiency anemia whose anemia is not corrected with oral therapy. Required dose can be calculated (3.5 mg iron/g of hemoglobin) or obtained from tables in the PDR. For IV use, INFeD may be diluted in 0.9% sterile saline. Do not add to solutions containing medications or parenteral nutrition solutions.

Dosing

Adult

Test dose: 0.5 mL IV/IM (slowly over 1 min if IV); observe for 60 min before providing additional medication
Usual adult dose: 2 mL/d (100 mg iron); may be given until anemia is corrected
Pediatric

<5 kg: Not established
5-10 kg: 50 mg iron (1 mL) IV/IM
10-50 kg: 100 mg iron (2 mL) IV/IM
>50 kg: Administer as in adults

Interactions

Absorption is enhanced by ascorbic acid; interferes with tetracycline absorption; food and antacids impair absorption

Contraindications

Documented hypersensitivity; microcytic anemias without laboratory documentation of iron deficiency; absence of iron deficiency anemia; anemia that cannot be corrected with oral therapy of iron

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Administer IM INFeD in upper outer quadrant of buttock using a Z-track technique to avoid tattooing; anaphylaxis, death, delayed serum sickness, fever, chest pain, respiratory arrest, wheezing and dyspnea, abdominal pain with nausea and vomiting, seizures, dizziness and disorientation, arthralgia, and back pain may occur; teratogenic effects are reported with high doses in some animals

Follow-up

Further Outpatient Care

- Monitor patients with iron deficiency anemia on an outpatient basis to ensure that there is an adequate response to iron therapy and that iron therapy is continued until after correction of the anemia to replenish body iron stores. Follow-up also may be important to treat any underlying cause of the iron deficiency.
- Response to iron therapy can be documented by an increase in reticulocytes 5-10 days after the initiation of iron therapy. The hemoglobin concentration increases about 1 g/dL weekly until normal values are restored. These responses are blunted in the presence of sustained blood loss or coexistent factors that impair hemoglobin synthesis.

Transfer
Transfer of a patient rarely is required for treatment of simple iron deficiency anemia; however, it may be necessary to identify the etiology of the anemia, such as occult blood loss undetected with chemical testing of stool specimens, for identification of a source of bleeding that requires endoscopic examinations or angiography or for treatment of an underlying major illness (eg, neoplasia, ulcerative colitis).

**Deterrence/Prevention**

- Certain populations are at sufficiently high risk of iron deficiency to warrant consideration for prophylactic iron therapy. These include pregnant women, women with menorrhagia, consumers of a strict vegetarian diet, infants, adolescent females, and regular blood donors.
- Pregnant women have been given supplemental iron since World War II. Often, this is administered in all-purpose capsules containing vitamins, calcium, and iron. If the patient is anemic (hemoglobin <11 g/dL), administer the iron at a different time of day than calcium because calcium inhibits iron absorption. The practice of routinely administering iron to pregnant females in affluent societies has been challenged recently; however, provide prophylactic iron therapy during the last one half of pregnancy, except in settings where careful follow-up for anemia and methods for measurement of serum iron and ferritin are readily available.
- Iron supplementation of the diet of infants is advocated. Premature infants require more iron supplementation than term infants. Infants weaned early and fed bovine milk require more iron because the higher concentration of calcium in cow milk inhibits absorption of iron. Usually, infants receive iron from fortified cereal. Additional iron is present in commercial milk formulas.
- Iron supplementation in populations living on a largely vegetarian diet is advisable because of the lower bioavailability of inorganic iron than heme iron.

**Complications**

- Iron deficiency anemia diminishes work performance by forcing muscles to depend, to a greater extent than in healthy individuals, upon anaerobic metabolism. This is believed to be due to deficiency in iron-containing respiratory enzymes rather than anemia.
- Severe anemia due to any cause may produce hypoxemia and enhance the occurrence of coronary insufficiency and myocardial ischemia. Likewise, it can worsen the pulmonary status of patients with chronic pulmonary disease.
- Defects in structure and function of epithelial tissues may be observed in iron deficiency. Fingernails may become brittle or longitudinally ridged with development of koilonychia (spoon-shaped nails). The tongue may show atrophy of the lingual papillae and develop a glossy appearance. Angular stomatitis may occur with fissures at the corners of the mouth. Dysphagia may occur with solid foods, with webbing of the mucosa at the junction of the hypopharynx and the esophagus (Plummer-Vinson syndrome); this has been associated with squamous cell carcinoma of the cricoid area. Atrophic gastritis occurs in iron deficiency with progressive loss of acid secretion, pepsin, and intrinsic factor and development of an antibody to gastric parietal cells. Small intestinal villi become blunted.
Cold intolerance develops in one fifth of patients with chronic iron deficiency anemia and is manifested by vasomotor disturbances, neurologic pain, or numbness and tingling.

Rarely, severe iron deficiency anemia is associated with papilledema, increased intracranial pressure, and the clinical picture of pseudotumor cerebri. These manifestations are corrected with iron therapy.

Impaired immune function is reported in subjects who are iron deficient, and there are reports that these patients are prone to infection; however, evidence that this is directly due to iron deficiency is not convincing because of the presence of other factors.

Children deficient in iron may exhibit behavioral disturbances. Neurologic development is impaired in infants and scholastic performance is reduced in children of school age. The IQ of school children deficient in iron is reported as significantly less than their nonanemic peers. Behavioral disturbances may manifest as an attention deficit disorder. Growth is impaired in infants with iron deficiency. All these manifestations improve following iron therapy.

**Prognosis**

Iron deficiency anemia is an easily treated disorder with an excellent outcome; however, it may be caused by an underlying condition with a poor prognosis, such as neoplasia. Similarly, the prognosis may be altered by a comorbid condition such as coronary artery disease.

**Patient Education**

- Physician education is needed to ensure a greater awareness of iron deficiency and the testing needed to establish the diagnosis properly. Physician education also is needed to investigate the etiology of the iron deficiency.
- Public health officials in geographic regions where iron deficiency is prevalent need to be aware of the significance of iron deficiency, its effect upon work performance, and the importance of providing iron during pregnancy and childhood. The addition of iron to basic foodstuffs is employed in these areas to diminish the problem.
- For excellent patient education resources, visit eMedicine's Blood and Lymphatic System Center and Esophagus, Stomach, and Intestine Center. Also, see eMedicine's patient education articles Anemia and Celiac Sprue.

**Miscellaneous**

**Medicolegal Pitfalls**

- Failure to investigate the etiology of the iron deficiency anemia causing a delayed or missed diagnosis of neoplasm
- Giving iron to patients who have a microcytic iron-overloading disorder (eg, thalassemia, sideroblastic anemia)
- Failure to promptly and adequately treat a patient with iron deficiency anemia who is symptomatic with a comorbid condition such as coronary artery disease
• Anaphylaxis pursuant to the use of parenteral iron therapy in patients who should be treated with oral iron

Special Concerns

• Special effort should be made to identify and treat iron deficiency during pregnancy and early childhood because of the effects of severe iron deficiency upon learning capability, growth, and development.

• The addition of iron to basic foodstuffs in affluent nations where meat is an important part of the diet is of questionable value and may be harmful. The gene for familial hemochromatosis (HFe gene) is prevalent (8% of US white population). Excess body iron is postulated to be important in the etiology of coronary artery disease, strokes, certain carcinomas, and neurodegenerative disorders because iron is important in free radical formation.