CASE STUDY

88 IRON DEFICIENCY ANEMIA

For the Patient Case for this case study, see the printed book.

DISEASE SUMMARY

Definitions

Anemia is not a disease but a complication of a disease process or abnormality in body function. It can be defined in both qualitative and quantitative terms. Qualitatively, *anemia* is defined as an abnormally low number of circulating red blood cells (RBCs) or level of hemoglobin, or both, resulting in subnormal oxygen-carrying capacity of the blood. Quantitatively, anemia is present in adults if the hematocrit is <41% in males and <37% in females. Because iron is an essential component of hemoglobin, a key molecule responsible for the transport of oxygen by RBCs, iron deficiency leads to decreased hemoglobin synthesis, consequent anemia, and impairment of oxygen delivery to tissues throughout the body. *Iron deficiency anemia* (IDA) is a type of anemia that is characterized by microcytic (i.e., small), hypochromic (i.e., pale) RBCs in the peripheral blood and low hemoglobin, hematocrit, total body iron stores, serum iron, and serum ferritin concentrations. The pallor of RBCs in IDA reflects the associated low hemoglobin content.

Prevalence

Iron deficiency is the most prevalent single deficiency state worldwide and affects persons of all ages. Furthermore, IDA is the most common type of anemia internationally, occurring in both developing and developed countries. It has been estimated that approximately one fifth of the world population is iron deficient.

In the United States, high-risk groups include women of childbearing age—especially pregnant or lactating women and those who lose excessive amounts of blood during menses (a condition known as *menorrhagia*)—infants, children, adolescents, vegetarians, and regular blood donors. Females demonstrate a higher frequency of iron deficiency (13.9%) than do males (8.3%). The incidence of IDA is as high as 6% in females but only 4% in males. ***Pregnant women appear to be the single largest population with IDA.*** Some reports indicate that as many as half of all pregnant women may be iron deficient. Also, in the United States, 720,000 children (≈9%) aged 1–2 years are estimated to be iron deficient, of whom 240,000 (≈3%) are anemic.

Race per se probably has no significant effect upon the occurrence of IDA. However, because diet and socioeconomic factors play a role in the prevalence of iron deficiency, IDA is more frequently observed in people of various racial backgrounds living in poverty. Those at greatest risk are African-American females living in poor urban areas.

An increased prevalence of iron deficiency has also been observed in overweight children.

Significance

Mild IDA usually does not cause complications and IDA is rarely life-threatening. However, if untreated, IDA can become severe and lead to serious health problems. A common complication of moderately severe IDA is fatigue. Iron deficiency in pregnant women can increase the risk for preterm delivery and delivering a low–birth-weight baby. Iron deficiency in children can result in both physical and mental developmental delays (e.g., walking and talking), behavioral disturbances, and failure to grow and thrive. Neurologic development is impaired in infants and scholastic performance is reduced in children of school age. The IQ (i.e., intelligence quotient) of schoolchildren deficient in iron is reported as significantly less than that of non-anemic peers. Recent research has also demonstrated that teens who were iron deficient as infants are likely to score lower on cognitive and motor tests. Low scores result even if iron deficiency is treated in infancy. Behavioral disturbances may manifest as attention deficit disorder. If IDA is not treated, permanent mental and behavioral problems are potential complications.

IDA causes the nails to become thin, brittle, coarsely ridged, and spoon-shaped or concave—a condition known as *koilonychia*. The tongue may develop a red, smooth, glossy appearance and become extremely sore (i.e., *glossitis*). Painful fissures may also develop at the corners of the mouth (i.e., *angular stomatitis*). Intolerance to cold develops in approximately one fifth of patients with long-term IDA. Many iron-deficient individuals develop a bizarre, compulsive eating disorder known as *pica* in which patients crave abnormal, non-nutritional substances (e.g., dirt, ice, clay, laundry starch, cardboard, hair) that are often not rich in iron. *Restless leg syndrome* (characterized by restlessness and sensory disturbances, such as numbness and uncomfortable tingling, that lead to an irresistible urge to move the legs) may occur at night, especially among the elderly.

In people with coronary artery disease (i.e., narrowing of the arteries that deliver blood to heart muscle, most commonly from the buildup of lipids and scar tissue in blood vessel walls), unchecked IDA can lead to angina (i.e., chest pain caused by poor oxygen delivery to the heart). Likewise, IDA can also worsen the status of patients with chronic pulmonary disease such as emphysema.

Occasionally, a condition known as *Plummer-Vinson syndrome* may develop, especially in women older than 60 years of age. This condition is characterized by the development of webs of tissue in the esophagus, a chronically sore throat, and dysphagia (i.e., difficulty swallowing). Severe IDA may cause an increase in intracranial pressure, papilledema (i.e., swelling of the optic discs), stroke, and cranial nerve palsies. Recent studies have also documented that IDA is associated with cancer of the gastrointestinal tract, especially esophageal cancer.

Causes and Risk Factors

In the United States, IDA results primarily from increased demands for iron, loss of iron through bleeding, and, occasionally, dietary deficiency of iron. ***The most common causes of IDA in the United States and other developed countries are pregnancy—in which there is a physiologic increase in the demand for iron—and chronic, often undetected, blood loss.*** During pregnancy, the expansion of the mother's blood volume requires approximately 500 mg additional iron and the growing fetus requires approximately 360 mg for new blood and muscle production. In the postnatal period, lactation requires approximately 1 mg iron every day.

Normal growth patterns of the infant, child, and adolescent also place extra demands on the body for iron. Blood volume increases during these periods of significant growth and development with a greater need for iron. Iron requirements are proportionately higher in infancy from 3–24 months than at any other age. During infancy, the two primary causes of IDA are low serum iron concentrations at birth from maternal deficiency and a diet consisting mainly of cow's milk, which does not provide significant amounts of absorbable iron. Adolescents are susceptible to IDA because of high requirements during growth spurts, dietary deficiencies, and menstrual loss of blood.

A common cause of IDA in the United States is blood loss, especially slow and persistent gastrointestinal (GI) blood loss. A diagnosis of IDA demands a search for a source of GI bleeding when more common sites of blood loss have been excluded. Blood loss of 2–4 mL/day is sufficient to cause iron deficiency.

In females of reproductive age, menorrhagia is a common cause of IDA. A normal monthly menstrual blood loss is approximately 50 mL or 21 mg (i.e., 0.7 mg/day). However,

menstrual loss may be five times normal (3.5 mg/day). To maintain an adequate amount of stored iron, women with heavy menstrual losses must absorb 3–4 mg iron from the diet every day. This amount of dietary iron is rarely absorbed, and women with severe menorrhagia will almost always develop IDA without iron supplementation.

In men and postmenopausal women, IDA is usually caused by GI blood loss associated with bleeding gastric and duodenal ulcers, long-term use of high-dose aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), and certain types of cancer, especially esophageal, gastric, colon, kidney, and bladder cancers. Other sources of chronic blood loss include erosive esophagitis, uterine fibroids (i.e., non-cancerous smooth muscle tumors of the uterus), colon polyps, and bleeding hemorrhoids.

Still other noteworthy causes of IDA in the United States include:

- surgical procedures that decrease stomach acidity, intestinal transit time, and absorption of iron (e.g., gastrectomy)
- insufficient dietary intake of iron (meat, eggs, and whole-grain foods are excellent sources of iron)
- chronic renal failure and hemodialysis
- chronic loss of iron in the urine (i.e., *hemoglobinuria*) as may occur with hemolysis of RBCs (e.g., trauma-induced lysis of RBCs in patients with a prosthetic heart valve or drug-induced hemolysis as occurs with penicillin, methyldopa, chlorpromazine, isoniazid, and quinidine use)
- extensive chronic GI disease (e.g., celiac disease or Crohn disease) in which iron absorption is impaired
- overuse of prescription-strength stomach acid blockers known as *proton pump inhibitors (PPI)*. This adverse effect of PPI develops because PPI raise the gastric pH and more alkaline gastric juices reduce the absorption of iron.

Helicobacter pylori infections of the GI tract also have been found to cause IDA and may be related to the ability of the bacteria to both promote bleeding ulcers and impair iron absorption.

Disease Summary Question 1. Would a duodenectomy and duodenitis contribute to iron deficiency anemia primarily by directly decreasing the absorption of iron or by indirectly decreasing iron absorption via decreasing acidity?

Disease Summary Question 2. Why are vegetarians at high risk for iron deficiency anemia?

Disease Summary Question 3. Provide the brand names of *four* commonly advertised proton pump inhibitors.

Pathophysiology

Iron is vital for all living organisms because it is essential for critical metabolic processes including oxygen transport, synthesis of deoxyribonucleic acid (DNA), and electron transport. Iron equilibrium is regulated carefully to ensure that sufficient dietary iron is absorbed to compensate for daily body iron losses. Quantitatively, body loss of iron is as important as absorption in terms of maintaining iron balance. Persistent errors in maintaining iron balance lead to either an iron deficiency or iron overload.

Total body iron ranges between 2–4 g—approximately 50 mg/kg in men and 35 mg/kg in women. Most iron (70–95%) is present as a component of hemoglobin in circulating RBCs. One mL packed RBCs (i.e., 2.0–2.8 mL whole blood depending on hematocrit) contains approximately 1 mg iron. Another 200–400 mg iron is present in muscle myoglobin, cytochromes, and iron-containing enzymes, such as catalase and peroxidase. Aside from circulating RBCs, the major location of body iron is within storage sites—as ferritin (a rapidly usable form of stored iron), hemosiderin, or within macrophages. The range of stored iron is wide (up to 2 g). Approximately one in four women in the United States has no stored iron whatsoever.

Iron is one of the most carefully conserved nutrients in the human body. When RBCs become old and are lysed in the spleen after circulating for 100–120 days, iron is released

from the heme component of hemoglobin. Iron is then recycled and either reused in the bone marrow for the production of hemoglobin and healthy new RBCs or stored in the liver, spleen, and skeletal muscle.

In general, body iron remains balanced if absorption of iron is constant at 1 mg/day (supplied by a typical Western diet) and iron loss is consistent at 1 mg/day. The average American diet contains 10–15 mg iron per day. Approximately 10% of this amount (i.e., 1.0–1.5 mg) is absorbed primarily in the duodenum but to some degree in the stomach, ileum, jejunum, and colon. Dietary iron present as heme is efficiently absorbed (up to 20%) but non-heme iron less so (1–5%), largely due to the presence of phosphates (e.g., in junk foods), tannates, phytates, oxalates, and carbonates. The iron that is absorbed enters the circulation, combines with a plasma protein known as *apotransferrin*, and produces the iron-protein complex *transferrin*. Transferrin transports iron through the blood to the bone marrow for new hemoglobin synthesis and RBC production or to the liver, spleen, and other tissues for storage. Small amounts of iron—approximately 1 mg—are normally lost through exfoliation of skin cells or lining cells in the GI tract every day.

IDA occurs when the demand for iron exceeds supply, developing slowly through three overlapping stages. In stage I, the body's iron stores are depleted. Red blood cell production proceeds normally and the hemoglobin content of RBCs is normal. In stage II, iron transport to bone marrow is diminished, resulting in the production of RBCs with subnormal amounts of hemoglobin. Stage III begins when small (i.e., microcytic), hemoglobin-deficient (i.e., hypochromic) cells enter the bloodstream in significant numbers, replacing RBCs that have been removed from the circulation. Clinical manifestations of IDA appear in stage III.

Symptoms of IDA develop gradually and do not become troublesome until the total serum hemoglobin concentration has fallen below 10 g/dL in women and 12 g/dL in men. Some of the clinical manifestations of IDA have been attributed to a deficiency of hemoglobin and impaired oxygen transport (e.g., skin pallor, rapid heart rate, and shortness of breath with exertion). However, increasing evidence suggests that many symptoms are the result of a deficiency of iron-dependent enzymes and proteins (e.g., esophageal webs, altered behavior, poor scholastic performance).

Recommended daily allowances of iron for different subpopulations of people are shown in Disease Summary Table 88.1.

Disease Summary Question 4. Why does the recommended daily allowance for iron increase so significantly in girls after age 13 years and decrease so significantly in women after age 50 years?

Disease Summary Table 88.1 Recommended Daily Allowances for Iron

Subpopulation	Recommended Daily Allowance (mg)
Infants, birth–6 months	0.27
Children, ages 7–12 months	11
Children, ages 1–3 years	7
Children, ages 4–8 years	10
Children, ages 9–13 years	8
Boys, ages 14–18 years	11
Girls, ages 14–18 years	15
Men, >18 years	8
Women, ages 19–50 years	18
Women, >50 years	8
Pregnant women, ages 14–50 years	27

Adapted with permission from Baron RB. Nutrition. In: McPhee SJ, Papadakis MA, Tierney LM Jr., eds. 2007 Current Medical Diagnosis and Treatment. 46th Ed. New York: McGraw-Hill, 2007;Table 29-2:1282. Original source: Institute of Medicine. Committee on Use of Dietary Reference Intakes in Nutrition Labeling. Dietary reference intakes: Guiding principles for nutrition labeling and fortification. National Academy of Sciences, Washington DC, 2003, Table C-3.

Diagnosis: Clinical Manifestations and Laboratory Tests

Although the diagnosis of IDA is definitively established by laboratory blood tests that show an iron-deficient state, a carefully obtained patient history can facilitate recognition of the disorder. Furthermore, patient history can be useful both in establishing cause and in estimating its duration. Often patients can provide a distinct point in time when clinical manifestations first appeared, providing an estimate of the duration of IDA.

A dietary history is especially important. Vegetarians are likely to develop IDA if their diet is not supplemented with iron. Elderly patients may become iron-deficient due to poor economic circumstances. Half of all patients with moderate IDA develop a craving for ice or other non-nutritive substances, which further promotes identification of an iron-deficient state.

Since bleeding is currently a common cause of IDA in the United States, patients often report a history that includes:

- hematuria (i.e., blood in the urine)
- hematemesis (i.e., vomiting blood)
- hemoptysis (i.e., coughing up blood)
- melena (i.e., blood in the stools)

Unless menstrual flow changes significantly, female patients do not usually seek medical attention. Because of the marked differences among women with regard to menstrual blood loss (i.e., 10–250 mL per menses), the thorough healthcare provider often queries the patient about a specific history of blood clots, cramping, and the use of multiple tampons and pads.

Clinical manifestations of IDA develop gradually. Early symptoms include easy fatigability (i.e., lack of stamina), weakness, and dyspnea (i.e., shortness of breath) with mild physical exertion. Pale mucous membranes, earlobes, palms, and conjunctiva are common early signs, as are tachycardia (i.e., abnormally fast heart rate), palpitations (i.e., sense of a racing, pounding heart), and tachypnea (i.e., abnormal rapid breathing rate) with exertion. These abnormal clinical signs are readily identified with a physical examination.

Progression of IDA causes more severe abnormalities such as koilonychia, glossitis, angular stomatitis, dysphagia associated with dry mouth and the development of esophageal webs, splenomegaly (i.e., abnormally large spleen), and both physical and mental developmental delays in infants and children. Other clinical manifestations consistent with a diagnosis of IDA include the following:

- irritability
- light-headedness or dizziness
- difficulty maintaining concentration
- frontal (i.e., in the forehead) headaches
- mental confusion, disorientation, or memory loss in elderly patients
- restless leg syndrome in elderly patients
- chest pain in patients with coronary artery disease
- a new and transient heart murmur
- cold hands and feet
- poor appetite in infants and children
- blue tinge to sclerae (i.e., whites of the eyes)

Initial laboratory investigations are based on the presence of a decreased hematocrit and whole blood hemoglobin concentration. Additional measurements, however, are necessary to confirm the diagnosis and are shown in Disease Summary Table 88.2.

Serum ferritin level is a widely accepted and available measurement of iron status that has been used for the past three decades and is superior to other measurements. A serum ferritin value <30 ng/mL is a highly reliable indicator of iron deficiency and a low ferritin concentration is one of the first laboratory results that is abnormal when iron is deficient.

A more recently developed index of iron levels is the serum transferrin receptor (sTfR). Transferrin receptors are membrane glycoproteins that function as the entrance point to developing RBCs for circulating transferrin. By using the ratio of sTfR to serum ferritin concentration, estimation of body iron stores is becoming more accurate and reliable. However, ***low serum iron and ferritin concentrations and an elevated TIBC (i.e., total iron-binding capacity) remain diagnostic for iron deficiency.***

Disease Summary Table 88.2 Laboratory Tests and Expected Findings in Iron Deficiency

Laboratory Test	Expected Finding for Iron Deficiency
Hemoglobin concentration	Low
Hematocrit	Low
Mean corpuscular volume (MCV)	Low
Mean corpuscular hemoglobin concentration (MCHC)	Low
Plasma iron concentration	Low
Total iron-binding capacity (TIBC)	High
Serum ferritin concentration	Low
Serum B12 concentration	Normal
Serum folate concentration	Normal
Serum bilirubin concentration	Normal
Free erythrocyte protoporphyrin (FEP) concentration	High
Transferrin saturation	Low
White blood cell count	Normal
Platelet count	High with bleeding Low in infants and children

Source: Conrad ME. Iron deficiency anemia. eMedicine website. Available at: www.emedicine.com/med/topic1188.htm. Date accessed: October 2006.

As IDA progresses, more and more RBCs in the peripheral blood appear microcytic and hypochromic. With further progression, mild *anisocytosis* (i.e., variation in RBC size) and *poikilocytosis* (i.e., variation in RBC shape) develop. Severe IDA is characterized by severely hypochromic cells in the peripheral blood smear, occasional target cells, hypochromic cigar-shaped cells, and small numbers of nucleated RBCs. *Target cells* are abnormal RBCs that are characterized by a densely stained center surrounded by a pale, unstained ring that is encircled by a dark, irregular band. As the name implies, these cells closely resemble a target. A peripheral blood smear from a patient with severe IDA is illustrated in Disease Summary Figure 88.1.

When the healthcare provider suspects that digestive tract bleeding is causing IDA, tests are conducted to determine the underlying cause of GI bleeding. These include the following:

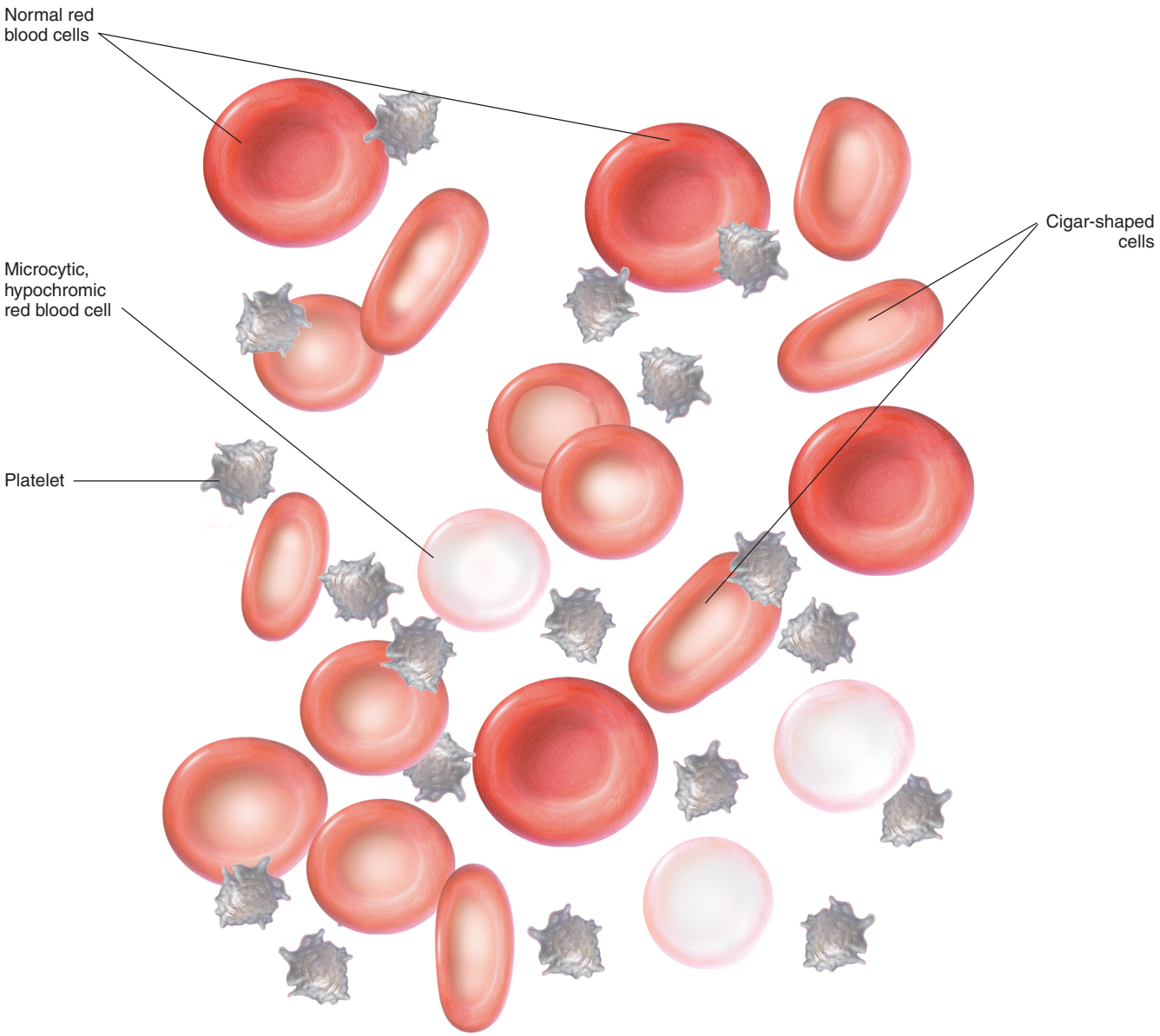
- *fecal occult blood test* in which stool samples are examined for blood
- *colonoscopy* in which the colon is carefully inspected for polyps or other sources of bleeding. The patient is sedated and a thin, flexible, lighted tube equipped with a miniature video camera is inserted into the rectum and guided through the colon.
- *upper GI endoscopy* in which the esophagus and upper stomach are carefully examined for ulcers and other sources of bleeding. A thin, flexible, lighted tube fitted with a miniature video camera is passed down the throat and into the stomach.

A bone marrow aspirate can also be diagnostic for iron deficiency. The absence of stainable iron in a specimen of bone marrow tissue permits establishment of a diagnosis of iron deficiency without other laboratory tests.

Appropriate Therapy

Treatment of IDA in children and adults is directed toward administering supplemental iron, increasing intake of dietary iron with iron-rich foods, and, if necessary, controlling chronic blood loss. If blood loss persists, no iron replacement treatment is likely to be effective. Surgery may be required to stop the bleeding and correct the underlying defect.

A positive response to a therapeutic trial of iron therapy is diagnostic for IDA. In fact, the most conclusive evidence for a diagnosis of IDA is an increase in hemoglobin of 1–2 g/dL after iron therapy is begun. ***Ferrous sulfate, 325 mg three times by mouth daily, is currently the preferred therapy for IDA in adults because it is both economical and effective.*** For



Disease Summary Figure 88.1
Illustration of peripheral blood smear in iron deficiency anemia. Characteristic clinical features include variations in red blood cell size and shape and the presence of severely hypochromic, microcytic, and cigar-shaped erythrocytes. (Image provided by the Anatomical Chart Company.)

children and depending on the severity of IDA, daily total doses of 3–6 mg/kg divided into three equal doses are appropriate. Maximum absorption of iron occurs when the medication is taken on an empty stomach, but many patients cannot tolerate the side effects and may need to take it with food. Milk, antacids, caffeinated beverages, and high-fiber foods (e.g., raw green vegetables and whole-grain foods) interfere with the absorption of iron and should not be taken simultaneously. Conversely, vitamin C (e.g., orange juice) promotes absorption. Patient compliance is improved by introducing the medicine slowly in a gradually increasing dose with food. Initial iron replacement therapy of 150–200 mg/day is appropriate, and some patients markedly respond to a dose of only 60 mg/day. Alternatively, in cases of poor tolerance, one pill of ferrous sulfate can be taken at bedtime on an empty stomach. Once therapy is initiated, individuals report a rapid decrease in fatigue and weakness. An appropriate therapeutic response is a return of the hematocrit halfway to normal within 3 weeks and full return to normal after 2 months. When the serum ferritin concentration reaches 50 ng/mL, adequate replacement of

iron has occurred. To replenish iron stores, iron therapy should continue for a minimum of 3 months (and, in some cases, for as long as 2 years) after restoration of normal hematologic values. Failure of the patient to respond is usually the result of non-compliance, although some patients absorb iron poorly. Other reasons for failure to respond include incorrect diagnosis and ongoing GI blood loss that exceeds the rate of new RBC production.

Although only 70% as effective as ferrous sulfate, carbonyl iron can be used as a substitute. Since the amount of iron contained in each tablet is less, claims have been made that there is less GI irritation and discomfort, prompting its use where ferrous sulfate is causing intestinal symptoms and in patients with a peptic ulcer or gastritis.

Indications for parenteral iron are emergency treatment of IDA, intolerance to oral iron, lack of a response to oral iron, GI disease that precludes the use of oral iron, or persistent blood loss that cannot be corrected. Because of the potential for anaphylactic shock, parenteral iron therapy should be used only when IDA is persistent after a reasonable course of oral therapy. Sodium ferric gluconate causes a lower incidence of anaphylaxis than does iron dextran, and no deaths have been reported with the use of this preparation. A dose of 1 mg iron for every mL packed RBCs below normal is given and then another 1 g is administered to replenish stored iron (usually a total dose of 1.5–2.0 g). The entire dose may be given as an intravenous infusion over 4–6 hours. A test dose of a dilute solution is given first and the patient is carefully observed for anaphylaxis during the entire infusion.

Restriction of activity usually is not required. However, patients with moderately severe IDA and significant cardiopulmonary disease are instructed to limit their activities until anemia has been controlled.

Prevention of iron deficiency is a primary concern in infants and children. Breastfeeding, avoidance of cow's, goat's, and soy milk to age 1 year, iron supplementation to 4–6 months of age in infants who are not breastfed or only partially breastfed, and use of iron-fortified formulas and cereals after 6 months of age are recommended. In the second year, a diet rich in iron-containing foods and use of iron-fortified vitamins will help prevent iron deficiency.

Disease Summary Question 5. Why do milk and antacids decrease the absorption of iron in the gastrointestinal tract?

Disease Summary Question 6. Describe, in a stepwise fashion, the sequence of pathophysiologic mechanisms that causes the marked decrease in blood pressure, widespread tissue swelling, and difficulty breathing associated with systemic anaphylaxis.

Disease Summary Question 7. Can you think of a hypothetical situation in which, in addition to ferrous sulfate, the primary care provider may also prescribe an oral contraceptive to manage the patient's iron balance?

Serious Complications and Prognosis

Iron deficiency anemia is an easily treated disorder with an excellent outcome when the underlying cause is successfully managed. However, even among patients with incurable disease states, management of IDA with iron therapy can increase both comfort level and overall quality of life. In most cases, symptoms of IDA are relieved within the first few days of treatment and clinical indicators of body iron return to normal in 2 months. Since IDA may recur, regular follow-up is encouraged.

The most serious potential complications of IDA include:

- preterm delivery and delivery of a low–birth-weight infant when pregnant women are iron deficient
- physical and mental delays in development among young children
- adverse effects on IQ and scholastic performance among school-age children
- development of attention deficit disorder in school-age children
- significant worsening in health status of patients with coronary artery disease or chronic pulmonary disease

- dysphagia from the development of esophageal webs
- a compulsive eating disorder of abnormal non-nutritive substances (pica)
- stroke
- development of esophageal cancer

Most people can prevent IDA by adhering to recommended daily allowances for iron and eating foods high in iron. Iron-rich foods include meats (especially beef liver), fish, poultry, eggs, whole-grain and iron-fortified cereals, breads, and pastas. Significant amounts of iron are also found in raisins, nuts, kidney beans, peas, lentils, spinach, tofu, and figs.

Suggested Readings

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