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INTRODUCTION

The diagnosis of iron deficiency (low iron stores, as measured by iron studies or other testing) is a major public health goal and an important aspect of the care of many adults. This topic will review the causes of iron deficiency in adults and an approach to the diagnostic evaluation. Treatment of iron deficiency in adults is discussed separately. (See "Treatment of iron deficiency anemia in adults".)

The evaluation and management of iron deficiency in other populations is presented in separate topic reviews:

- Children– (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis" and "Iron deficiency in infants and children <12 years: Treatment".)
- Adolescents – (See "Iron requirements and iron deficiency in adolescents".)
- Pregnancy – (See "Anemia in pregnancy" and "Nutrition in pregnancy", section on 'Iron'.)

EPIDEMIOLOGY

Iron deficiency, as defined by one of the tests listed below (see 'Diagnosis' below), affects a large proportion of the world's population, especially women of childbearing age, children, and individuals living in low- and middle-income countries. The absolute prevalence of iron deficiency depends on the population studied.

In all of the studies that evaluate the scope of the problem, iron deficiency is more prevalent than iron deficiency anemia (low hemoglobin or hematocrit caused by iron deficiency), and females are affected more than males.

As examples:

- A systematic analysis of the global burden of anemia from 1990 to 2010 found that the prevalence of iron deficiency anemia (and anemia overall) decreased but remained significant [1]. For females, iron deficiency anemia was present in nearly 20,000 per 100,000 population (approximately one in five). For both decades and for virtually every population (males, females, different regions of the world), iron deficiency accounted for the largest proportion of cases of anemia. These findings are illustrated in the figure (figure 1).
- Data from the United States (US) general population have been collected periodically from various groups such as the National Health and Nutrition Examination Survey (NHANES) and the Centers for Disease Control (CDC) [2,3]. The prevalence of iron deficiency and iron deficiency anemia from one such survey

from 2002 is summarized in the figure (figure 2). Subsequent surveys on selected populations suggest that the percentages of individuals with iron deficiency have not declined substantively over time [4].

- A 2020 study from England found higher rates of iron deficiency without anemia, using ferritin levels in 4451 non-anemic individuals over 50 years of age who were enrolled in the English Longitudinal Study of Ageing [5]. Of these, 389 (8.7 percent) were found to be iron-deficient, defined as a ferritin <30 ng/mL (<30 mcg/L). The prevalence of non-anemic iron deficiency was higher in women than men (10.9 versus 6.3 percent). Other features associated with a higher likelihood of non-anemic iron deficiency included alcohol consumption on more than one day per week and elevated C-reactive protein. In this study, non-anemic patients with a low ferritin had increased mortality compared to those with normal ferritin.

Considerations regarding screening are discussed below. (See 'Screening (asymptomatic individuals)' below.)

The greater prevalence of iron deficiency and iron deficiency anemia in females of childbearing age is attributed to menstruation and childbirth, as discussed in detail separately. (See "Anemia in pregnancy", section on 'Iron deficiency'.)

Iron deficiency anemia in older adults is also greater than that seen in the general population. In a series of 190 adults in the community >65 years of age with anemia, 12 percent were due to iron deficiency [6].

Racial and ethnic disparities in iron deficiency are also present. Analysis of over 60,000 women in the Hemochromatosis and Iron Overload Screening (HEIRS) study in the United States found the following prevalence of iron deficiency (defined as ferritin <15 ng/mL and transferrin saturation <10 percent) [7]:

- Hispanic Americans – 5.1 percent
- Black Americans – 4.3 percent
- Asian Americans – 2.1 percent
- White Americans – 2.0 percent

The prevalence of iron deficiency was 5.2 percent in Native Americans and 3.1 percent in Pacific Islanders, although fewer participants from these groups were included in the study [7]. Carrier status for a hereditary hemochromatosis variant in the *HFE* gene (C282Y or H63D) did not correlate with the prevalence of iron deficiency in any racial or age group in HEIRS participants.

Blood donors in the general population typically have slightly lower iron stores than non-donors, although this rarely translates to iron deficiency anemia [8]. Various blood donor series from a number of North American and European countries have estimated the rate of subclinical iron deficiency in the range of 5 to 15 percent [9,10]. This has led some experts to consider screening for iron deficiency and/or recommending iron supplementation for blood donors, as discussed separately. (See "Blood donor screening: Overview of recipient and donor protections", section on 'Anemia'.)

As discussed separately, iron deficiency is very common in non-anemic women early in pregnancy (prevalence as high as 42 percent in one series), suggesting that these women were likely iron deficient prior to becoming pregnant. (See "Anemia in pregnancy", section on 'Epidemiology'.)

CAUSES AND RISK FACTORS FOR IRON DEFICIENCY

The major causes of iron deficiency are decreased dietary intake, reduced absorption, and blood loss. In adults in resource-rich countries, dietary intake is almost always adequate, and it is usually reasonable to assume that the cause is blood loss until proven otherwise, with the implied need to search for and identify the cause. (See 'Search for source of blood and iron loss' below.)

Blood loss — The major cause of iron deficiency in resource-rich countries is blood loss, either overt or occult [11-16].

Overt bleeding is obvious and not difficult for the clinician to recognize, often by history alone:

- Traumatic hemorrhage
- Hematemesis or melena
- Hemoptysis
- Heavy menstrual bleeding
- Pregnancy and delivery
- Hematuria

Other causes of blood loss that may be overlooked include:

- Frequent blood donation
- Excessive diagnostic blood testing
- Underestimation of the degree of heavy menstrual bleeding
- Pregnancy and lactation, with a greater likelihood as the number of pregnancies increases
- Occult bleeding, typically gastrointestinal (eg, gastritis, malignancy, angiodysplasia) but may also include hemolysis with urinary losses
- Exercise-induced blood loss, often due to occult gastrointestinal bleeding (see "Exercise-related gastrointestinal disorders", section on 'Gastrointestinal bleeding')
- Gastrointestinal parasites (eg, hookworm, whipworm), especially in developing countries

Typical iron loss during pregnancy has been estimated at approximately 1000 mg for pregnancy, delivery, and nursing. Menstrual blood losses account for approximately 1 mg of iron loss per day. (See "Anemia in pregnancy", section on 'Iron deficiency'.)

Typical iron loss during hemodialysis may be as much as 2 g per year, which is highly likely to produce iron deficiency without supplementation. (See "Diagnosis of iron deficiency in chronic kidney disease" and "Treatment of iron deficiency in hemodialysis patients".)

The likelihood that iron deficiency is due to an occult gastrointestinal tumor has been illustrated in several case series; gastrointestinal disorders that reduce iron absorption are discussed below (see 'Reduced iron absorption' below):

- In a 2012 series of 621 patients with definite or probable iron deficiency anemia, cancer and high-risk adenomas were identified in 51 of 310 (16 percent) of the individuals who underwent endoscopy [17].

- In a 2005 series of 148 adults (median age, 66 years) with chronic iron deficiency who underwent endoscopy, 18 (12 percent) were found to have a malignant tumor [18].

- In a 2002 report from the first National Health and Nutrition Examination Survey and Epidemiologic Follow-up Study (NHANES I) that included 9024 adults, 18 new gastrointestinal malignancies were identified [19].

Iron deficiency was a strong predictor of gastrointestinal cancer in men and postmenopausal women but not in premenopausal women, with the following rates of gastrointestinal cancer detection over a two-year period:

- Premenopausal women with iron deficiency – 0 of 442
- Men and postmenopausal women with iron deficiency – 5 of 274 (2 percent)
- Men and postmenopausal women without iron deficiency – 11 of 5733 (0.2 percent)

These findings reinforce the importance of identifying the cause of blood loss, especially in men and postmenopausal women. (See 'Search for source of blood and iron loss' below.)

Reduced iron absorption — Iron is absorbed in the upper gastrointestinal tract; the duodenum is the site of maximal absorption [20]. Reduced absorption of iron is an uncommon cause of iron deficiency, especially in healthy individuals and in regions of the world where there is access to an iron-replete diet.

However, several factors determine the efficiency of iron absorption, and certain medical conditions may interfere with normal uptake of dietary iron. The most clinically important are disorders that affect the mucosal cells responsible for iron absorption, such as celiac disease, atrophic gastritis, *Helicobacter pylori* infection, and bariatric surgery. Inherited disorders that interfere with iron absorption are very rare.

Sources of reduced iron absorption may be considered in individuals with gastrointestinal symptoms or those who do not have an adequate response to oral iron supplementation. Regardless of whether reduced iron absorption is documented, a source of bleeding should be excluded. (See "Treatment of iron deficiency anemia in adults", section on 'Response to iron supplementation' and 'Search for source of blood and iron loss' below.)

Diet — Dietary heme iron (iron from meat rather than plant sources) is better absorbed than non-heme iron. A review of published studies that evaluated vegetarians and non-vegetarians found that those who consumed a vegetarian diet were more likely to be iron deficient [21]. However, non-heme iron is available from a wide array of vegetables and supplemented grains and cereals, as summarized in the table (table 1).

A number of foods may impair iron absorption such as tannates, phosphates, phytates (mineral-binding compounds found in whole grains and seeds), and foods high in calcium (table 2).

It would be very difficult to develop iron deficiency solely due to these dietary factors, but they may contribute to iron deficiency in the setting of blood loss, or, less commonly, extremely low intake [16].

Celiac disease/atrophic gastritis/H. pylori — Celiac disease (also called gluten-sensitive enteropathy or nontropical sprue) is a disorder of small bowel inflammation triggered by exposure to gluten in susceptible individuals. It predominantly affects White populations of northern European ancestry, with a prevalence of approximately 1 in 70 to 1 in 300 (0.3 to 1 percent) in these populations. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".)

- **Celiac disease** – Celiac disease can contribute to anemia by several mechanisms, including iron deficiency, reduced absorption of supplemental iron, and malabsorption of other nutrients required for red blood cell (RBC) production including vitamin B12, folic acid, and copper [22]. There may also be a component of anemia of chronic disease/anemia of inflammation (ACD/AI) as well as blood loss, although the contribution (if any) of gastrointestinal blood loss from celiac disease to iron deficiency is unclear [22]. Various reports have commented on the unexpected presence of celiac disease in individuals with iron

deficiency and vice versa. As an example, in a series of 102 patients diagnosed with celiac disease in a northern European hospital, 70 had anemia as the presenting feature, and 34 of these 70 (approximately half) were premenopausal women, who might otherwise be thought to have iron deficiency on the basis of heavy menses [23]. In another series of 200 Scandinavian patients with anemia who underwent testing for celiac disease, 10 (5 percent) were found to be positive by serologic testing confirmed by intestinal biopsy [24].

- **Autoimmune gastritis and *H. pylori*** – Gastritis related to an autoimmune mechanism (eg, anti-parietal cell antibodies) or *H. pylori* has also been implicated in causing iron deficiency [25,26]. The following studies demonstrate that these conditions may be more common than previously appreciated:

  - In a series of 373 individuals with iron deficiency that included 356 premenopausal women, 69 (18 percent) had anti-parietal cell antibodies and 24 of 167 (14 percent) had *H. pylori* antigen in stool. Only 1 percent had endomysial antibodies suggesting celiac disease [27]. Of the subset of 26 with anti-parietal cell antibodies who underwent upper gastrointestinal endoscopy, 12 had a histologic diagnosis of autoimmune gastritis confirmed. Histologic diagnosis correlated with higher antibody levels (>100 units/mL); none of the individuals with antibody levels <20 units/mL who had endoscopy for other reasons was found to have gastritis.

  - In a series of 150 patients (mostly adults) with iron deficiency anemia, refractoriness to oral iron treatment was noted in 24 of 34 (71 percent) with anti-parietal cell antibodies and autoimmune gastritis, and in 15 of 22 (68 percent) with *H. pylori* (as well as all eight with celiac disease) [28].

  - In another series of 71 patients with iron deficiency anemia who did not have an obvious source of blood loss and underwent upper and lower endoscopy, diagnoses related to reduced absorption included atrophic gastritis in 19 (27 percent) and *H. pylori* in 13 (18 percent), as well as celiac disease in four (6 percent) [14].

The possibility of these conditions should be reviewed, and testing obtained, in individuals with unexplained iron deficiency, especially those at increased risk based on demographic features and those for whom oral iron therapy is ineffective. (See "Treatment of iron deficiency anemia in adults", section on 'Approaches to lack of response'.)

Bariatric surgery — Iron needs to be conjugated to vitamin C, amino acids, or sugars in the presence of gastric acid to protect it from the alkaline secretions in the proximal jejunum, which will otherwise convert the iron to ferric hydroxide (rust), which is unabsorbable. Bariatric surgery includes a number of procedures that promote weight loss by limiting gastric reservoir capacity and/or shortening the length of functional small intestine, which causes malabsorption. Procedures that bypass the duodenum such as roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD-DS) have the greatest risk of causing iron deficiency because they reduce the site of maximal absorption and in some cases reduce gastric acid availability. (See "Bariatric procedures for the management of severe obesity: Descriptions" and "Regulation of iron balance", section on 'Intestinal iron absorption'.)

Routine iron supplementation and monitoring of iron status with repletion as needed is used after most bariatric surgeries. (See "Bariatric surgery: Postoperative nutritional management".)

Medications — An acidic gastric environment facilitates absorption of iron, especially non-heme iron. However, reduced gastric acidity by itself is unlikely to cause clinically significant iron deficiency in an individual

with an adequate dietary iron intake and a normally functioning gastrointestinal tract.

Medications that reduce gastric acidity, especially proton pump inhibitors (PPIs), have been proposed to reduce iron absorption. This is mainly based on observational studies, which suggest a dose-response relationship between the dose of PPI (or duration of use) and risk of iron deficiency [29,30]. However, these studies indicate association rather than causation; individuals taking a PPI are more likely to have gastrointestinal conditions that lead to bleeding or reduced iron absorption, such as those listed above. (See 'Celiac disease/atrophic gastritis/H. pylori' above.)

If an individual with iron deficiency is taking a PPI, antacid, or histamine receptor blocker, we do not attribute iron deficiency to the medication without performing an evaluation for bleeding or reduced iron absorption as indicated for the individual. Further, we take the opportunity to re-evaluate whether the PPI is actually indicated, and we review the symptoms that led to PPI use and make sure they are properly evaluated. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders".)

Medications that increase the risk of gastrointestinal bleeding may cause iron deficiency (eg, nonsteroidal antiinflammatory drugs [NSAIDs], aspirin, anticoagulants). However, we do not attribute iron deficiency to these medications without also evaluating the underlying source of bleeding. (See 'Blood loss' above.)

Redistribution after erythropoietin/erythropoiesis-stimulating agents — A response to treatment with erythropoietin (EPO) for the anemia of chronic renal failure often leads to the discovery of absolute or functional iron deficiency (see 'Absolute versus functional deficiency' below) since the iron requirements generated by this response in the short term can usually not be met by mobilization of the iron stores alone [31]. This is a particular problem with maintenance hemodialysis. These individuals may lose an average of 2 g of iron per year, mainly from repeated blood testing and blood losses within the hemodialysis circuit [32]. Thus, iron deficiency will develop in almost all patients undergoing dialysis who are treated with EPO, as well as some individuals with chronic renal failure not receiving dialysis, unless supplemental iron is administered. This subject is discussed in detail in separate topic reviews. (See "Treatment of iron deficiency in nondialysis chronic kidney disease (CKD) patients" and "Treatment of iron deficiency in hemodialysis patients" and "Hyporesponse to erythropoiesis-stimulating agents (ESAs) in chronic kidney disease".)

EPO or other erythropoiesis-stimulating agents are also used for patients with cancer-associated anemia. The anemia may be multifactorial and include a component of bleeding and iron deficiency. In addition, functional iron deficiency due to hepcidin, the primary mediator of anemia of chronic disease/anemia of inflammation, may limit the availability of iron and the response to erythropoiesis-stimulating agent therapy in these patients, and those with borderline iron stores may rapidly develop more classic features of iron deficiency. Thus, iron status is routinely monitored, and supplementation provided in many cases. This subject is also discussed in detail separately. (See "Role of erythropoiesis-stimulating agents in the treatment of anemia in patients with cancer" and "Causes of anemia in patients with cancer".)

Urinary/pulmonary hemosiderosis — In some conditions, iron may be lost when there is shedding of iron-laden cells, especially over a prolonged period of time or multiple episodes.

- **Urinary** – Chronic or intermittent intravascular hemolysis with hemosiderin accumulation in urinary epithelial cells may lead to iron loss through urinary shedding of these cells. Examples include individuals with intensive athletic training, prosthetic heart valve-associated hemolysis, or paroxysmal nocturnal hemoglobinuria (PNH). (See "Overview of the management of patients with prosthetic heart valves",

section on 'Hemolytic anemia' and "Clinical manifestations and diagnosis of paroxysmal nocturnal hemoglobinuria", section on 'Hemolysis'.)

- **Pulmonary** – Pulmonary hemosiderosis, such as in individuals with diffuse alveolar hemorrhage or idiopathic pulmonary hemosiderosis may lead to iron loss through iron-laden alveolar or bronchial epithelial cells. These conditions also may cause a component of functional iron deficiency, in which iron is trapped in pulmonary macrophages. (See "Idiopathic pulmonary hemosiderosis" and "The diffuse alveolar hemorrhage syndromes".)

Inherited disorders/IRIDA

- **IRIDA due to *TMPRSS6* mutation** – Iron refractory iron deficiency anemia (IRIDA) is a rare inherited disorder in which absorption of oral iron is markedly impaired. IRIDA is caused by loss-of-function mutations of the TMPRSS6/matriptase 2 gene, which encodes a serine protease that cleaves membrane-bound hemojuvelin [33-42]. Membrane-bound hemojuvelin promotes hepcidin synthesis and impairs iron absorption in the gut; cleavage of membrane-bound hemojuvelin reduces hepcidin synthesis, increasing iron absorption. Loss of *TMPRSS6* function thus causes iron deficiency due to inappropriately high hepcidin levels, with markedly reduced iron absorption and increased sequestration of iron in macrophages [39,43-48]. (See "Regulation of iron balance", section on 'Hemojuvelin'.)

  In published case reports as well as our own experience, patients with IRIDA are not anemic at birth, and the clinical phenotype develops after the neonatal period (eg, after one month of age). Suspicion of IRIDA usually occurs during a pediatric routine evaluation. However, in some patients, the condition is recognized only in adulthood, either because the anemia is mild or because it has been misclassified. Patients present with mild hypochromic, microcytic anemia with very low serum iron levels and low transferrin saturation. Serum ferritin levels are mostly within the normal range or even slightly elevated following treatment with intravenous iron [39]. The diagnosis is pursued after elimination of causes of iron deficiency refractory to iron therapy such as celiac disease, *H. pylori* infection, autoimmune gastritis, or anemia of chronic disease/inflammation [34]. The diagnosis of IRIDA is confirmed by demonstrating biallelic mutation in *TMPRSS6*; testing laboratories are listed on the Genetic Testing Registry website.

- ***SLC11A2* mutation** – Iron deficiency anemia has also been described in individuals with mutations in the SLC11A2 gene, which encodes the divalent metal transporter DMT1 [49-53]. (See "Regulation of iron balance", section on 'Divalent metal transporter 1'.)

High-intensity athletics — Iron deficiency may be seen in some athletes due to gastrointestinal bleeding or reduced iron intake [54,55]. Other causes of anemia may also contribute. (See "Overtraining syndrome in athletes", section on 'Anemia and iron deficiency'.)

STAGES OF IRON DEFICIENCY

The development of iron deficiency, and the rapidity with which it progresses, depend on the individual's baseline iron stores, which are correlated with age, sex, and the steady state iron balance; as well as the degree, duration, and rapidity of iron or blood loss. (See "Regulation of iron balance".)

Normal body iron content — The normal body iron content in an adult is approximately 3 to 4 grams. The majority of iron is present in circulating red blood cells (RBCs), with additional iron in myoglobin and certain

enzymes, as well as iron in storage and transport forms (figure 3). Typical amounts of iron in these sites is as follows (table 3):

- RBCs – Approximately 2 g, corresponding to approximately 2000 mL (25 to 30 mL/kg) of RBCs
- Iron-containing proteins (eg, myoglobin, cytochromes, catalase) – Approximately 400 mg
- Plasma iron bound to transferrin – 3 to 7 mg
- Storage iron in the form of ferritin or hemosiderin – Approximately 0.8 to 1 g (men); approximately 0.4 to 0.5 g (women)

Storage iron in adult men has been estimated as being approximately 10 mg/kg, and is found mostly in the monocyte-macrophage system in the liver, spleen, and bone marrow. Adult women have less storage iron, depending upon the extent of menses, pregnancies, deliveries, lactation, and iron intake. In one study, 93 percent of women in the United States 20 to 45 years of age had iron stores of 5.5 ± 3.4 mg/kg, while the other 7 percent had an iron deficit of 3.9 ± 3.2 mg/kg [56]. Other estimates have suggested that up to 20 percent of menstruating women in the United States have absent iron stores [57]. The storage pool can be looked upon as a reserve of iron that can be utilized when there is increased need for hemoglobin synthesis, as in acute blood loss, growth in children and adolescents, pregnancy, lactation, and response to treatment with erythropoietin.

Progressive iron depletion — Iron deficiency occurs in several stages, as illustrated by progressive changes in laboratory findings (table 4) [11,15]. These stages are defined by the extent of depletion, first of iron stores and then of iron available for hemoglobin synthesis. Eventually, if negative iron balance continues, production of iron-deficient RBCs and anemia occurs.

In the first stage, iron stores can be totally depleted without causing anemia. Once these stores are depleted, there is still enough iron present in the body within the "labile" iron pool from the daily turnover of red cells for normal hemoglobin synthesis, but the individual becomes vulnerable to development of anemia should there be further iron losses. Some individuals with extremely low levels of serum ferritin, but without anemia, may have symptoms of fatigue or show decreased exercise tolerance at this stage.

Further loss of iron results in anemia, which is initially normocytic with a normal absolute reticulocyte count (table 4). This stage of iron deficiency is common in the United States. As noted above, it has been estimated that the proportion of menstruating women in the United States who have minimal or absent iron reserves is at least 20 percent and may be as high as 65 percent [58,59]. Common laboratory findings at this stage include:

- Low levels of ferritin and serum iron (Fe).
- Increased levels of transferrin (Tf; total iron binding capacity [TIBC]). If only transferrin concentrations are available, they can be converted to the TIBC (in mcg/dL) by multiplying the transferrin concentration (in mg/dL) by 1.389.
- Low percent saturation of transferrin (ie, Fe/TIBC or Fe/Tf, stated as a percent).
- Increased unsaturated iron binding capacity (UIBC = TIBC - Fe).

More profound deficiency results in the classical findings of anemia with RBCs that are hypochromic (low mean corpuscular hemoglobin [MCH]) and microcytic (low mean corpuscular volume [MCV]). Reticulocyte production cannot be increased in the setting of iron deficiency, and the reticulocyte count becomes inappropriately low (despite being in the "normal" range in many cases). It is worth noting, however, that other concomitant causes of anemia such as vitamin B12 deficiency may cause macrocytosis and obscure the microcytosis caused by iron deficiency. (See 'Diagnostic evaluation' below.)

The normal physiologic changes in response to iron deficiency produce a number of compensatory changes, including increased production of erythropoietin and reduced production of hepcidin, provided that renal function is normal and that the individual does not have an inflammatory condition that suppresses hepcidin production. The mechanisms of these changes are discussed in detail separately. (See "Regulation of iron balance".)

Absolute versus functional deficiency — We distinguish between absolute and functional iron deficiency.

- **Absolute iron deficiency** – Absolute iron deficiency refers to the absence of (or severely reduced) storage iron in the monocyte-macrophage system, including bone marrow, liver, and spleen.

- **Functional iron deficiency (also referred to as iron-restricted erythropoiesis)** – Some individuals have barely adequate iron stores for normal hematopoiesis, but the iron is not available for RBC production [60,61]. There are two main categories/mechanisms:

    - **Anemia of chronic disease/anemia of inflammation** – The most common mechanism is a block in iron release from macrophages back into the circulation, which occurs in the setting of inflammation and increased hepcidin production. Common causes include infections, malignancies, bariatric surgery (in certain individuals), or chronic medical conditions such as diabetes. Diagnosis and management are discussed in detail separately. (See "Anemia of chronic disease/anemia of inflammation".)

    - **Erythropoiesis-stimulating agents** – Another mechanism of functional iron deficiency is treatment with erythropoiesis-stimulating agents (erythropoietin and darbepoetin) in individuals with renal insufficiency or cancer and chemotherapy-induced anemia. In these cases, iron stores may be available but their release into the circulation may not be rapid enough to support the increased erythropoietic rate; thus, these individuals have insufficient iron stores to respond to the ESA; this is also referred to as iron restricted erythropoiesis. (See 'Redistribution after erythropoietin/erythropoiesis-stimulating agents' above.)

Thresholds for ferritin and transferrin saturation in absolute and functional iron deficiency are discussed below. (See 'Diagnosis' below.)

CLINICAL MANIFESTATIONS

Symptoms of anemia — The usual presenting symptoms in adults with iron deficiency are primarily due to anemia. The same symptoms may also be present in those with severely reduced iron stores and extremely low serum ferritin who are not anemic. Typical symptoms include [16]:

- Fatigue
- Pica (Pagophagia)
- Restless legs syndrome
- Headache
- Exercise intolerance
- Exertional dyspnea
- Weakness

These may be present in varying degrees and may not be appreciated at all until after iron deficiency is identified and treated. Many patients recognize in retrospect that they had fatigue, weakness, exercise

intolerance, and/or pica (see 'Pica and ice craving' below) only after successful iron repletion.

The classic presentation pattern in a patient without comorbidities is a multigravid woman who presents with tiredness and fatigue and a complete blood count (CBC) that shows anemia with low MCV (eg, hemoglobin 8 g/dL, MCV 75 fL) and a peripheral blood smear that shows microcytic, hypochromic RBCs (picture 1). Iron studies are likely to show low iron in the range of 10 mcg/dL, low ferritin (below 30 ng/mL), and increased transferrin (around 400 mcg/dL) or high TIBC, with a low calculated transferrin saturation (TSAT; below 20 percent). Such a patient is likely to have a brisk response to iron therapy. It is also important to consider the possibility of gastrointestinal blood loss, even in a menstruating woman.

Pica and ice craving — Pica refers to a desire for or compulsion to eat substances not fit as food; the term is derived from the Latin word for magpie (*Pica pica*), a bird that gathers non-food objects [62]. These substances may include earth substances such as clay or dirt (geophagia); paper products including wallpaper or toilet paper; starches including corn starch, laundry starch, fabric softener sheets, or raw rice or pasta (amylophagia); or ice (pagophagia). Other reported substances have included chalk, ashes, charcoal, coffee grounds, baby powder, and paint chips. The specific substances that are craved may depend on what is available and what is considered culturally acceptable [63,64]. The craving for these non-food substances may be intense. In pregnant women, pica may also be misinterpreted as food cravings unrelated to iron status.

Overall, pica may be seen in many clinical settings and is not considered specific for iron deficiency. However, pagophagia (pica for ice) is considered quite specific for iron deficiency [63,65,66]. It may be present in patients who are not anemic and responds rapidly to treatment with iron (disappears during iron infusions), often before any increase is noted in the hemoglobin concentration. In one study of 55 unselected patients with iron deficiency anemia secondary to gastrointestinal blood loss, pica was present in 32 (58 percent), which manifested as pagophagia in 28 (51 percent of the total; 88 percent of those with pica) [65].

Pica may also contribute to iron deficiency by reducing iron absorption, depending on the substance ingested (see 'Reduced iron absorption' above). Its mechanism in individuals with iron deficiency is not well understood.

Beeturia — Beeturia is a phenomenon in which the urine turns red following ingestion of beets. Beeturia is increased in individuals with iron deficiency but the finding is not specific for iron deficiency. It has been noted in approximately 10 to 14 percent of healthy individuals following ingestion of beets and in as much as 49 to 80 percent of individuals with iron deficiency [67-69].

Beeturia is caused by increased intestinal absorption and subsequent excretion of the reddish pigment betalaine (betanin) present in beets. Betalaine, a redox indicator, is decolorized by ferric ions, which presumably explains the predisposition to beeturia when adequate amounts of iron are not available for decolorization of this pigment. (See "Urinalysis in the diagnosis of kidney disease", section on 'Red to brown urine'.)

Restless legs syndrome — Restless legs syndrome (RLS), also called Willis-Ekbom disease, is a disorder in which there is an unpleasant or uncomfortable urge to move the legs during periods of inactivity. The discomfort is relieved by movement, often instantaneously. A number of changes in the central nervous system have been correlated with RLS. Of these, reduced iron in the central nervous system has been a consistent finding, regardless of total body iron stores. (See "Clinical features and diagnosis of restless legs syndrome and periodic limb movement disorder in adults", section on 'Pathophysiology'.)

RLS is common in the general population, in some series affecting 5 to 15 percent of adults, especially in White populations. Iron deficiency may be one of the more common causes of RLS, and RLS may be one of the more common clinical manifestations of iron deficiency. As an example, in a series of 251 patients with iron deficiency anemia referred to a community-based hematology practice, the prevalence of clinically significant RLS was 24 percent, approximately nine times higher than that seen in the control population [70].

While overall findings linking RLS to iron deficiency are not conclusive, they warrant the measurement of hemoglobin and iron parameters in individuals who present with this symptom, and administration of iron when stores are low. A 2018 guideline from the International Restless Legs Syndrome Study Group provides a consensus on intervention with oral or intravenous iron [71]. Some clinicians will give a trial of iron therapy even when iron parameters are normal as some will experience a reduction in symptoms. This subject is discussed in depth separately. (See "Treatment of restless legs syndrome and periodic limb movement disorder in adults", section on 'Iron replacement' and "Treatment of iron deficiency anemia in adults", section on 'Iron deficiency without anemia'.)

Other findings — An association between iron deficiency and hearing loss in adults has been reported; the observation was based on a retrospective cohort study involving over 300,000 adults, in which the prevalence of combined hearing loss was 1.6 percent and the prevalence of iron deficiency was 0.7 percent [72]. Compared with controls, iron-deficient individuals had an adjusted odds ratio (OR) for combined hearing loss of 2.4 (95% CI 1.9-3.0). The mechanism of the association is not known, and we do not perform a formal audiologic evaluation unless the patient reports difficulty with hearing.

Findings on examination — The physical examination in individuals with iron deficiency (with or without anemia) may be normal or it may reveal one or more of the following findings [16,73]:

- Pallor
- Dry or rough skin
- Atrophic glossitis with loss of tongue papillae, which may be accompanied by tongue pain or dry mouth (picture 2 and picture 3) [74]
- Cheilosis (also called angular cheilitis) (picture 4 and picture 5)
- Koilonychia (spoon nails) (picture 6 and picture 7)
- Esophageal web, which may be accompanied by dysphagia (eg, Plummer-Vinson or Patterson-Kelly syndrome; rare)
- Alopecia (rare) in especially severe cases [75]
- Chlorosis (pale, faintly green complexion; extremely rare)

The more severe of these findings, including chlorosis and Plummer-Vinson syndrome, which were more common during the early 1900s, have virtually disappeared [76,77]. Patients with more severe anemia may have tachycardia, a cardiac murmur, or (rarely) hemodynamic instability [16].

For individuals with gastrointestinal blood loss, the stool may show overt or occult blood. However, absence of blood in the stool does not eliminate the possibilities of gastrointestinal bleeding or iron deficiency (or the need to evaluate for a source of gastrointestinal bleeding when appropriate), because bleeding may be intermittent.

DIAGNOSTIC EVALUATION

Overview of evaluation — The possibility of iron deficiency should be addressed in the following adult populations:

- Virtually all adults with unexplained anemia, especially those with new-onset anemia or microcytic anemia without reticulocytosis. (See "Approach to the child with anemia" and "Diagnostic approach to anemia in adults".)

- Individuals without anemia who have any of the typical clinical findings such as pica (especially pagophagia [ice-craving]) or restless legs syndrome (RLS). (See 'Clinical manifestations' above.)

- Pregnant women. (See "Anemia in pregnancy".)

- Individuals with chronic kidney disease who have anemia or who are receiving hemodialysis or an erythropoiesis-stimulating agent (ESA). (See "Diagnosis of iron deficiency in chronic kidney disease" and "Treatment of anemia in nondialysis chronic kidney disease".)

For these patients, it is reasonable to evaluate the complete blood count (CBC) and red blood cell (RBC) indices, especially mean corpuscular volume (MCV), and take a history for possible causes of blood loss. For those with microcytic or normocytic anemia, a reticulocyte count should be used to determine whether there is decreased RBC production, which is consistent with iron deficiency; increased RBC destruction (hemolysis); or blood loss. Review of the peripheral blood smear is likely to provide valuable information regarding the characteristic morphologies seen in iron deficiency anemia (picture 1) versus other causes of anemia. The history, CBC, RBC indices, and findings on the peripheral blood smear usually allow the clinician to make a presumptive diagnosis of iron deficiency anemia. (See "Diagnostic approach to anemia in adults", section on 'Evaluation based on CBC/retic count'.)

There are two complementary ways to confirm (or exclude) the diagnosis of iron deficiency: iron studies (see 'Iron studies (list of available tests)' below) and assessment of the response to a trial of iron therapy (see 'Response to a therapeutic trial of iron' below). In the vast majority of individuals, iron studies should be obtained. The results help to distinguish iron deficiency from other conditions, document the severity of the deficiency (if present), and provide a baseline prior to initiating iron administration. Exceptions may include individuals who do not have access to this testing (eg, in low-resource settings) or in routine obstetric practice. (See "Nutrition in pregnancy", section on 'Iron'.)

Even before the diagnosis of iron deficiency is confirmed, patients with suspected iron deficiency should be evaluated for the source of the deficiency. In many developed countries, iron deficiency is more likely to be due to blood loss in menstruating or pregnant females and adults of either sex, and it is more likely to have a dietary component in children and menstruating women, reflecting an imbalance between physiologic demands and intake, and in vegetarians. In the less developed world, parasitic infestations may be a significant contributing issue [78]. The evaluation may include a thorough history and physical examination. Additional testing is discussed below, including colonoscopy if iron deficiency is confirmed. (See 'Search for source of blood and iron loss' below.)

The gold standard for documenting iron deficiency is an iron stain (Prussian blue stain) of a bone marrow aspirate smear to assess iron stores in bone marrow macrophages and erythroid precursors (sideroblasts) on marrow spicules. Lack of stainable iron in erythroid precursors as well as bone marrow macrophages is consistent with iron deficiency, whereas in anemia of chronic disease, increased stainable iron is seen in marrow macrophages but stainable iron is absent or reduced in erythroid precursors (picture 8). However,

as noted in the following sections, other less-invasive and less-expensive methods are available and effective for confirming or excluding iron deficiency in the vast majority of cases. In some cases where there is an obvious other explanation for anemia and the patient is undergoing bone marrow testing, iron deficiency may be a surprise finding. In these cases, it is important to ensure that proper controls and confirmatory testing is performed.

Findings on CBC — Changes in the CBC occur in proportion to the severity of iron deficiency and tend to lag behind changes in iron studies; reduced storage iron precedes anemia. In turn, a slight decline in hemoglobin (usually 1 to 2 g/dL) precedes microcytosis (table 4). Thus, in early iron deficiency and in many individuals in high-resource settings, the CBC may be relatively normal.

As iron deficiency progresses and the individual becomes anemic, the following findings may be seen on the CBC:

- Low red blood cell (RBC) count (typical RBC count for a patient with a hemoglobin of 9 g/dL would be approximately 3 million cells per microL)
- Low hemoglobin and hematocrit
- Low absolute reticulocyte count
- Low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH)

The low RBC count is useful for distinguishing iron deficiency from thalassemia in an individual with markedly microcytic anemia and an abnormal blood smear. (See 'Differential diagnosis' below.)

The platelet count may be increased in iron deficiency anemia. This is thought to result from stimulation of platelet precursors by erythropoietin. (See "Approach to the patient with thrombocytosis", section on 'Causes of thrombocytosis'.)

The low MCV and MCH are reflected on the peripheral blood smear by microcytic, hypochromic RBCs (picture 1). As anemia progresses, increasingly abnormal forms (poikilocytosis) may be seen.

Automated counting of reticulocytes has also allowed measurement of reticulocyte indices (similar to RBC indices) that include reticulocyte volume, reticulocyte hemoglobin content, and reticulocyte hemoglobin concentration [79]. These are not used in routine practice, but some of the newer electronic counters can provide the result, which may be helpful as supporting information or for research [80]. In some studies, a reticulocyte hemoglobin content of <26 pg/cell has correlated well with the finding of iron deficiency [81,82]. (See "Automated hematology instrumentation", section on 'Automated counting of reticulocytes'.)

Iron studies (list of available tests) — Iron deficiency anemia is characterized by reduced or absent iron stores and increased levels of transferrin proteins that facilitate iron uptake and transport to RBC precursors in the bone marrow (table 4). Of these iron studies, ferritin remains the most useful test if low. Otherwise, patients require iron and total iron binding capacity (TIBC), from which one calculates transferrin saturation (TSAT) [15,16,73]. In order to avoid the inconvenience and cost of an additional office visit, our practice is to order all three tests (serum ferritin, iron, and TIBC) in nearly all patients. It is important to consider the entire clinical picture when deciding which tests to order and when evaluating test results.

Expected results of these and other tests in adults with iron deficiency are as follows:

- **Serum iron** – Iron can be measured in serum (preferred) or plasma. The test measures circulating iron, most of which is bound to the transport protein transferrin. Serum iron is low in iron deficiency as well as in anemia of chronic disease/anemia of inflammation (ACD/AI). This is because levels of serum iron depend on the efficiency of iron recycling by bone marrow and reticuloendothelial macrophages, which is reduced in both conditions. Serum iron can also fluctuate with dietary intake and normal diurnal variation. By itself, low serum iron is not diagnostic of any condition but must be evaluated in light of other tests such as transferrin saturation and ferritin. As serum iron may be transiently affected by absorption of dietary or pharmacologic iron, it is recommended that the sample be drawn after an overnight fast. (See 'Differential diagnosis' below.)

- **Serum transferrin** – Transferrin is a circulating transport protein for iron. It is increased in iron deficiency but can be decreased in ACD. Transferrin can also be reported as TIBC. The transferrin concentration (in mg/dL) can be converted to the TIBC (in mcg/dL) by multiplying by 1.389 [73].

- **Transferrin saturation** – Transferrin saturation (TSAT) is the ratio of serum iron to TIBC: (serum iron ÷ TIBC x 100). In iron deficiency, iron is reduced and TIBC is increased, resulting in a lower transferrin saturation. Normal values are in the range of 25 to 45 percent [83,84]. Values below 10 percent are common in individuals with iron deficiency, and a cutoff of below 19 percent is generally used to screen for iron deficiency, although other thresholds may be used in some settings such as pregnancy (see 'Pregnant women' below and "Anemia in pregnancy"). Because the TSAT is a ratio, in principle, an increase in the serum iron (eg, due to hemolysis or recent ingestion of an iron tablet) can raise the value, even in an individual who has iron deficiency and an increased TIBC.

- **Serum ferritin** – Ferritin is a circulating iron storage protein that is increased in proportion to body iron stores. However, ferritin is also an acute phase reactant (see "Acute phase reactants") that can increase independently of iron status in disorders associated with inflammation, infection, liver disease, heart failure, and malignancy [85]. The ferritin concentration that predicts the absence of marrow iron is debated. While many sources use a cutoff level of 12 to 15 ng/mL (99 percent specific but only 57 percent sensitive), our practice is to use a cutoff of 30 ng/mL, which is supported by bone marrow correlations and international guidelines [86,87]. The sensitivity and specificity for a cutoff at 30 ng/mL is estimated to be 92 percent and 98 percent, respectively [88]. A very low ferritin level is diagnostic of iron deficiency, but a higher ferritin level may be "falsely normal" and cannot be used to eliminate the possibility of iron deficiency in individuals with comorbidities. (See 'Diagnosis' below.)

- **Soluble transferrin receptor (sTfR) and sTfR-ferritin index** – Soluble transferrin receptor (sTfR), also called circulating transferrin receptor or serum transferrin receptor, is a circulating protein derived from cleavage of the membrane transferrin receptor on bone marrow erythroid precursor cells. Its concentration in serum is directly proportional to erythropoietic rate and inversely proportional to tissue iron availability, similar to serum transferrin [89]. Thus, iron-deficient patients generally have increased levels of sTfR, with reference ranges determined by the individual laboratory performing the testing. Different laboratories may report sTfR as mg/L or as nmol/L. sTfR is not used in routine practice but can be helpful in complex cases (see 'Patients with inconclusive initial testing or comorbidities' below). The major advantage of sTfR is that it reflects overall erythropoiesis, which is increased in iron deficiency. However, sTfR can be elevated in patients with hemolysis or with administration of erythropoiesis-stimulating agents (ESAs).

  sTfR-ferritin index is calculated as the ratio of the sTfR (in mg/L) to the logarithm of the serum ferritin (in mcg/L): (sTfR ÷ log[ferritin]). The sTfR reflects erythropoiesis, while the ferritin reflects the tissue iron

stores; thus, a high sTfR-ferritin index (eg, above 2 to 3) is very likely to be a sign of iron deficiency due to increased erythropoietic drive and low iron stores. This index may be especially useful for population-based studies and for distinguishing between iron deficiency anemia and anemia of chronic disease/anemia of inflammation (ACD/AI) (see 'Differential diagnosis' below) because sTfR is increased in iron deficiency and normal in ACD/AI, whereas ferritin is decreased in iron deficiency and normal-to-increased in ACD [15,56,90-93]. Patients with ACD/AI are likely to have an sTfR-ferritin index <1, whereas those with isolated iron deficiency or iron deficiency plus ACD/AI are likely to have an sTfR-ferritin index >2.

Some studies have shown the serum ferritin to be equally useful as the sTfR or the sTfR-ferritin index if the serum ferritin is low [94-96]. (See 'Patients with inconclusive initial testing or comorbidities' below.)

- **RBC protoporphyrin and RBC zinc protoporphyrin** – In iron deficiency, intestinal zinc absorption increases, and zinc is incorporated into protoporphyrin in developing RBCs. Thus, elevated erythrocyte (RBC) zinc protoporphyrin (eg, >80 mcg/dL) is consistent with iron deficiency. However, zinc protoporphyrin is not specific for iron deficiency as it may be elevated in inflammatory states, hemodialysis, and lead poisoning. These assays are not widely available or routinely used for diagnosing iron deficiency. Their role in the diagnosis of other disorders (eg, lead poisoning, porphyria) is discussed separately. (See "Childhood lead poisoning: Clinical manifestations and diagnosis" and "Lead exposure and poisoning in adults" and "Erythropoietic protoporphyria and X-linked protoporphyria", section on 'Erythrocyte protoporphyrin'.)

- **Reticulocyte hemoglobin content (CHr)** – The reticulocyte hemoglobin content (CHr, also called Ret-He) is available on some autoanalyzers and has the potential of providing very rapid information about iron status (at same time as CBC), especially in the presence of iron-restricted erythropoiesis [97]. Unlike the serum ferritin, the CHr is not influenced by inflammation. This parameter is used more extensively in individuals with chronic kidney disease; data are lacking regarding its role in managing anemia and iron therapy in other adults. (See "Diagnosis of iron deficiency in chronic kidney disease", section on 'Percent hypochromic HRCs and reticulocyte hemoglobin content'.)

- **Bone marrow iron stain** – Staining of the bone marrow aspirate smear for iron provides a qualitative assessment of iron in bone marrow cells (eg, macrophages, red blood cell precursors). Stainable bone marrow iron is considered the gold standard for assessing iron stores but is rarely required for diagnosis.

Appropriate use of these tests is described in the following sections. Additional information about the function of these proteins is presented separately. (See "Regulation of iron balance", section on 'Role of specific proteins'.)

Test interference — Recent intake of iron-rich foods or of oral iron supplements (even in multiple vitamins) may affect serum iron and therefore TSAT. For this reason, testing obtained in a fasting state are the most reliable. Ferritin concentration is not affected by food.

- Oral iron can transiently increase the serum iron concentration, with a dose-dependent peak at approximately four hours after the oral dose [98,99]. This could falsely increase the TSAT (which represents a ratio of serum iron to transferrin) and thus make an individual appear to have more normal iron stores than they actually have. Therefore, TSAT should not be drawn immediately after a morning dose of oral iron.

- Intravenous iron also increases serum iron and TSAT, and as a result, may alter the results of iron studies testing, similar to oral iron [100]. After a dose of intravenous iron, we typically wait and retest iron studies at the time of repeat CBC (eg, after approximately four weeks).

The use of tumor necrosis factor (TNF) inhibitors in individuals with chronic inflammatory conditions such as rheumatoid arthritis or inflammatory bowel disease appears to reduce the ferritin level (perhaps to a more accurate representation of iron stores) and increase the TSAT [101-103]. This may reflect the reduction in hepcidin and improved iron availability that these agents produce. In such cases, the serum ferritin is likely to be most representative of the level of iron stores despite its acute phase reactivity. (See "Anemia of chronic disease/anemia of inflammation", section on 'Cytokine effects' and "Anemia of chronic disease/anemia of inflammation", section on 'Iron studies'.)

Data evaluating the effects of recent blood transfusion on iron studies are limited. One study showed transient elevation of the serum iron and resultant TSAT within the first 24 hours of a blood transfusion [104]. However, other studies have shown only small, subclinical changes in iron parameters. As an example, a study that measured iron parameters 48 to 72 hours after a transfusion noted that in the individuals with low ferritin and TSAT prior to transfusion, 97 percent remained low after transfusion, and concluded that testing could be performed after transfusion [105]. If there is any doubt about the results of testing, it may be prudent to wait a day after transfusion to order iron studies (if indicated) in a patient who received a transfusion, based on a theoretical concern for test interference from hemolyzed cells [106-108].

In contrast to transient changes in iron studies related to the effects of a dose of iron on serum iron levels, true improvements in iron stores are expected if an iron-deficient individual receives supplemental iron and/or a blood transfusion. These improvements will be reflected in the iron studies (eg, serum ferritin and TSAT will increase, reflecting increased iron stores).

Sequence of testing

Individuals without comorbidities — Testing can be done using an iron studies panel, which includes serum iron, transferrin or total iron binding capacity (TIBC), calculated transferrin saturation (TSAT), and ferritin (algorithm 1). If one or more of the results is consistent with iron deficiency, this is typically sufficient to make the diagnosis. (See 'Diagnosis' below.)

Some clinicians prefer to order a single test rather than the entire iron studies panel. This is especially useful in individuals with a classic presentation, such as new onset microcytic anemia in a young woman with heavy menstrual bleeding or a multiparous women, and/or when there is a desire to limit testing, provided it would not be overly burdensome to return for additional testing if needed (if the first testing is inconclusive), or if additional testing can be ordered as an "add-on" if needed. In such cases, either the ferritin or the TSAT can be used as the initial test.

As noted above, the normal ferritin concentration ranges from 30 to 200 ng/mL (mcg/L) in otherwise healthy, iron-replete individuals (see 'Iron studies (list of available tests)' above). A ferritin level below 30 ng/mL is considered diagnostic of iron deficiency regardless of the patient's underlying condition or hemoglobin concentration. In individuals with anemia, a ferritin <30 ng/mL is sufficient to diagnose iron deficiency. However, a ferritin in the normal range does not exclude iron deficiency in an individual for whom there is a strong suspicion for iron deficiency. A TSAT <19 percent can also be used, as discussed below. (See 'Diagnosis' below.)

In contrast to a low ferritin, **a low serum iron cannot be used to diagnose or exclude iron deficiency**. Serum iron may be low in anemia of chronic disease/anemia of inflammation (ACD/AI) or increased by recent ingestion of an iron tablet. (See "Anemia of chronic disease/anemia of inflammation".)

Evidence to support the use of serum ferritin alone in appropriate patients includes a several observational studies in anemic adults comparing serum ferritin with the gold standard test (bone marrow stainable iron), as well as a 1992 systematic review [109]. In this review, serum ferritin radioimmunoassay had the greatest predictive value for iron deficiency (figure 4):

- A ferritin level ≤15 ng/mL had a 99 percent specificity for iron deficiency. Ferritin ≤15 ng/mL was highly specific in individuals with inflammatory states.
- A ferritin ≤15 ng/mL had a sensitivity of only 59 percent, meaning that a large proportion of individuals with iron deficiency would be missed.

Using a higher ferritin cutoff may improve sensitivity while maintaining a reasonable specificity. Various observational studies comparing ferritin levels with bone marrow stainable iron have found that a ferritin cutoff of <30 ng/mL provides a sensitivity in the range of 90 to 92 percent and a specificity in the range of 75 to 98 percent [86,110-112].

The relative performance of these iron studies tests in diagnosing iron deficiency compared with bone marrow iron staining is illustrated in the figure (figure 4) [15,113-116]. This demonstrates that ferritin has the best performance in individuals without comorbidities; however, ferritin is an acute phase reactant and can increase in the setting of an infection or obesity [113-115,117,118]. In such cases, TSAT may be more useful if low, or additional testing may be required. TSAT is a ratio of iron to TIBC, and it is most reliable when increased due to an increase in TIBC. TSAT can be falsely elevated by recent intake of iron-containing foods or an iron tablet. (See 'Iron studies (list of available tests)' above.)

Patients with inconclusive initial testing or comorbidities — Many individuals with iron deficiency or iron deficiency anemia in resource-rich countries do not have the classic presentation of anemia with a markedly decreased ferritin, either because they come to medical attention before severe deficiency develops or because they have multifactorial anemia (eg, iron deficiency and anemia of chronic disease). These patients may require additional assessment with a TSAT or other laboratory tests listed above (see 'Iron studies (list of available tests)' above), a therapeutic trial of iron, or (very rarely) bone marrow evaluation (algorithm 1).

In some patients the clinical situation is more complex, and additional evaluations and/or management considerations may predominate. Individuals with poorly controlled heart failure or diabetes may require a more thorough assessment of the reasons for poor control; individuals with other unexplained findings (eg, weight loss, adenopathy) may require further diagnostic testing for the cause of their symptoms. In such cases, it may be reasonable to defer a more extensive evaluation for iron deficiency and/or a therapeutic trial of iron until after these other issues are resolved.

The increase in ferritin level conferred by a chronic inflammatory state was demonstrated in a study that retrospectively reviewed records for several thousand patients who had measurements of ferritin as well as C-reactive protein (CRP) and albumin [119]. Median ferritin levels for increasing CRP were as follows:

- CRP <10 mg/L (least inflammation) – ferritin 85 mcg/L
- CRP 10 to 80 mg/L – ferritin 193 mcg/L
- CRP >80 mg/L (greatest inflammation) – ferritin 342 mcg/L

Lower serum albumin levels were also associated with higher serum ferritin levels.

Pregnant women — Pregnancy is associated with increased iron requirements, and iron deficiency is common, especially in individuals who are not iron replete before the pregnancy (eg, due to heavy menses, prior pregnancies, or lactation) and possibly in those who do not receive prenatal vitamins with iron. This subject, as well as our approach to screening for iron deficiency and evaluating anemia in pregnancy, is discussed in detail separately. (See "Anemia in pregnancy", section on 'Iron deficiency'.)

Response to a therapeutic trial of iron — A presumptive diagnosis of iron deficiency anemia may be made using a therapeutic trial of iron in a patient with anemia who has an obvious cause of iron deficiency such as individuals in resource-limited settings where it is not possible to obtain iron studies routinely, or in young women with heavy menstrual periods or pregnancy. In such cases, patients with iron deficiency anemia are expected to have a rapid and complete response to iron administration that includes resolution of symptoms, reticulocytosis, and normalization of hemoglobin level (typically by three weeks). (See "Treatment of iron deficiency anemia in adults", section on 'Response to iron supplementation'.)

However, as noted above, this approach should be reserved for individuals for whom other causes of anemia are unlikely (eg, it should be reserved for young, otherwise healthy individuals who do not have thalassemia) because it does not address other causes of anemia or the source of blood/iron loss, which is a crucial component of management. Further, it may be difficult to determine the reason(s) for a lack of response to iron if iron studies are not available. Additionally, administration of iron to an individual with thalassemia will worsen the existing iron overload commonly seen in this condition. Thus, it may be prudent to obtain iron studies to confirm the diagnosis even in cases where iron deficiency is considered extremely likely. For patients who wish to avoid a return appointment, we find it cost-effective to order iron studies and prescribe iron therapy at the same encounter, with plans to obtain additional testing only if the initial testing was inconclusive. (See 'Iron studies (list of available tests)' above.)

For those who do not respond to a therapeutic trial of iron, it is appropriate to obtain iron studies (eg, serum iron, transferrin/TIBC, and ferritin) as well as to investigate the reasons for a lack of response (table 5). (See 'Diagnostic evaluation' above and "Treatment of iron deficiency anemia in adults", section on 'Approaches to lack of response'.)

Diagnosis — We consider the diagnosis of iron deficiency to be confirmed by any one of the following findings in the appropriate clinical setting:

- Serum ferritin <30 ng/mL
- Transferrin saturation <19 percent, mostly used in patients for whom the ferritin is thought to be unreliable due to an inflammatory state
- Anemia that resolves upon iron administration
- Absence of stainable iron in the bone marrow (providing that adequate staining controls are performed)

Diagnosis should be accompanied by identification for the cause of iron deficiency and a strategy to treat the deficiency, if clinically indicated, as well as management of the underlying cause of the deficiency. For individuals with uncomplicated symptomatic iron deficiency or other comorbidities likely to benefit from iron repletion, the decision to treat with iron is straightforward. By contrast, there may be some individuals with significant comorbidities or other findings for whom it may be prudent to defer the correction of iron deficiency and avoid the gastrointestinal side effects of oral iron while addressing the patient's dominant findings. (See 'Search for source of blood and iron loss' below and "Treatment of iron deficiency anemia in adults".)

We diagnose functional iron deficiency in patients with chronic kidney disease or a malignancy who are candidates for treatment with an erythropoiesis-stimulating agent (ESA) if the serum ferritin is in the range of 100 to 500 ng/mL and the transferrin saturation is less than 20 percent (see 'Absolute versus functional deficiency' above). The implication is that these individuals would benefit from iron administration (typically, intravenous iron). (See "Diagnosis of iron deficiency in chronic kidney disease" and "Treatment of iron deficiency in nondialysis chronic kidney disease (CKD) patients" and "Treatment of iron deficiency in hemodialysis patients" and "Role of erythropoiesis-stimulating agents in the treatment of anemia in patients with cancer".)

By contrast, patients with anemia of chronic disease/anemia of inflammation (ACD/AI) generally are not diagnosed with functional iron deficiency because the major management intervention for these individuals is treatment of the underlying chronic condition. (See "Anemia of chronic disease/anemia of inflammation".)

Search for source of blood and iron loss — Iron deficiency almost always requires treatment, which includes iron administration **and** identification of the underlying cause, regardless of the severity of the deficiency and/or the presence of anemia [120]. Even before the diagnosis of iron deficiency is confirmed, individuals with suspected iron deficiency should be asked to provide information that might identify the source of the deficiency, which is more likely to be dietary in individuals in resource-poor settings and more likely to be due to blood loss in menstruating or pregnant females and adults of either sex.

This initial evaluation may involve the following:

- Dietary history for infants (eg, use of cow's milk rather than iron-supplemented formula or breastfeeding)
- Menstrual/pregnancy/lactation history for females (table 6)
- History of gastrointestinal blood loss, melena, hematemesis, and hematuria
- History of other gastrointestinal symptoms that might suggest celiac disease, autoimmune gastritis, or *H. pylori* infection
- History of multiple blood donations
- Marathon running [115]
- Use of non-steroidal anti-inflammatory drugs (NSAIDS) or anticoagulants
- Personal or family history of bleeding diathesis, including platelet disorders, von Willebrand disease, hereditary hemorrhagic telangiectasia
- Personal or family history of celiac disease, colon cancer, or other gastrointestinal disorders
- Review of the results of prior gastrointestinal evaluations (eg, routine colon cancer screening)
- Testing the stool for occult blood in adults 50 years of age or older

If iron deficiency is diagnosed, additional testing for possible occult gastrointestinal blood loss (eg, with endoscopy) is indicated for adults of all ages for whom a source of bleeding would be treated [121]. Several of the common causes, such as colonic and uterine cancer, have ominous prognoses unless discovered and treated promptly. An exception might be a very elderly individual who would prefer not to be treated or evaluated for malignancy. Evaluation for occult gastrointestinal bleeding and an approach to testing for gastrointestinal lesions is presented in detail separately. (See "Evaluation of occult gastrointestinal bleeding" and "Approach to acute lower gastrointestinal bleeding in adults" and "Evaluation of suspected small bowel bleeding (formerly obscure gastrointestinal bleeding)".)

The use of an anticoagulant or the presence of severe thrombocytopenia are important to note as they may contribute to bleeding. However, anticoagulation or thrombocytopenia do not diminish the importance of searching for the site(s) of bleeding such as a gastrointestinal or colonic lesion, as these hemostatic changes

are often more likely to unmask a bleeding source (and potentially result in earlier diagnosis) than to cause bleeding from a normal mucosa [122].

Celiac disease is important to identify if present; this can present at any age and symptoms may be absent (or may only be appreciated in retrospect). Celiac disease is also a common cause of a lack of response to iron therapy in patients with known iron deficiency because it interferes with iron absorption. (See 'Celiac disease/atrophic gastritis/H. pylori' above and "Treatment of iron deficiency anemia in adults", section on 'Response to iron supplementation'.)

As mentioned above, the prevalence of autoimmune gastritis may be even higher than that of celiac disease, and testing may be appropriate for anti-parietal cell antibodies as well [27]. (See 'Celiac disease/atrophic gastritis/H. pylori' above and "Metaplastic (chronic) atrophic gastritis".)

Differential diagnosis — The differential diagnosis of iron deficiency (without anemia) includes other causes of fatigue, pica, and restless legs syndrome (RLS). The differential diagnosis of iron deficiency anemia includes other causes of microcytic or hypoproliferative anemia (table 7). It is important to keep in mind that anemia may be multifactorial, and some individuals with other causes of anemia may also have iron deficiency.

- **Other causes of fatigue** – Other causes of fatigue are numerous and include a number of endocrine, cardiac, pulmonary, and other medical and psychiatric conditions. Like iron deficiency, symptoms may be vague and nonspecific, and in some cases, these individuals may have anemia of chronic inflammation (anemia of chronic disease). Unlike iron deficiency, individuals with these other conditions do not have laboratory evidence of low iron stores or a response to iron therapy. An approach to evaluating unexplained fatigue in adults is presented separately. (See "Approach to the adult patient with fatigue".)

- **Other causes of pica** – Other causes of pica include a primary eating disorder, which may be associated with developmental disabilities, and possibly micronutrient deficiencies (eg, zinc) and lead poisoning. As in patients with iron deficiency, patients with these conditions often are unaware of the source of the urge to eat non-food substances. Unlike iron deficiency, individuals with these other disorders do not have laboratory evidence of low iron stores or a response to iron therapy. (See "Eating disorders: Overview of epidemiology, clinical features, and diagnosis", section on 'Pica'.)

- **Other causes of restless legs syndrome** – Other causes of RLS include a number of neurologic conditions, pregnancy, leg cramps, and sleep disturbances. Like iron deficiency, these can cause a strong urge to move the legs. Unlike iron deficiency, these other conditions are not associated with globally decreased iron stores or evidence of iron deficiency in the peripheral blood. (See "Clinical features and diagnosis of restless legs syndrome and periodic limb movement disorder in adults".)

- **Other causes of anemia and/or microcytosis** – The other major causes of microcytic anemia are thalassemia and sideroblastic anemia; anemia of chronic disease/anemia of inflammation (ACD/AI) may also cause microcytic or normocytic anemia. Additional causes of anemia are listed in the table (table 7). (See "Microcytosis/Microcytic anemia", section on 'Causes of microcytosis'.)

    - **Thalassemia** – Thalassemias are inherited hemoglobin disorders associated with reduced production of alpha globin (alpha thalassemia), and beta globin (beta thalassemia). Like iron deficiency, thalassemia can cause microcytic anemia with hypochromic RBCs and target cells on the peripheral blood smear, the extent of which depends on the thalassemia phenotype (picture 9 and picture 10 and picture 11). Unlike iron deficiency anemia, individuals with thalassemia have

normal to increased RBC production and a normal to high RBC count on the CBC, characteristic findings on hemoglobin analysis, and often increased iron stores due to ineffective erythropoiesis and/or transfusions. (See "Clinical manifestations and diagnosis of the thalassemias".)

- **Sideroblastic anemia** – Sideroblastic anemias are characterized by the presence of ring sideroblasts on an iron stain of a bone marrow aspirate (picture 12). Causes are varied and include a number of rare inherited and acquired disorders, copper deficiency, and myelodysplastic/myeloproliferative neoplasms. Like iron deficiency, some of the inherited sideroblastic anemias can be microcytic. Unlike iron deficiency, these disorders are often associated with increased iron stores. While cells derived from the sideroblastic clone are microcytic, the overall mean corpuscular volume (MCV) is typically normal or elevated. By definition, individuals with sideroblastic anemia have iron present in the bone marrow aspirate because stainable iron is required to produce the ring sideroblast phenotype. (See "Sideroblastic anemias: Diagnosis and management".)

- **Anemia of chronic disease/anemia of inflammation (ACD/AI)** – ACD/AI is characterized by reduced production of RBCs due to an inflammatory block; iron is present in the reticuloendothelial system and bone marrow macrophages but cannot be supplied to developing RBCs due to high levels of hepcidin, which traps iron in storage cells. Like those with iron deficiency, patients with ACD/AI may have microcytic or normocytic anemia with a low serum iron and low transferrin (or TIBC). Unlike those with iron deficiency, individuals with ACD/AI have a chronic inflammatory state, often with increased storage iron (picture 8) and high levels of ferritin and other acute phase reactants. Distinction between iron deficiency anemia and ACD may be difficult, and in especially challenging cases may require calculation of the sTfR-ferritin index (see 'Iron studies (list of available tests)' above), bone marrow evaluation, therapeutic trial of iron, and/or repeat testing after additional treatment for an underlying inflammatory state. (See "Anemia of chronic disease/anemia of inflammation".)

- **Other anemias** – Other causes of anemia include renal failure, hypo- or hyperthyroidism, excessive alcohol use, and bone marrow disorders such as myelodysplastic syndromes (MDS). Lead poisoning rarely causes anemia unless it is severe. Like iron deficiency, these may develop gradually with nonspecific symptoms. Unlike iron deficiency, these anemias are associated with other laboratory findings rather than (or in addition to) evidence of decreased iron stores; in many cases the anemia is normocytic or macrocytic. MDS can be associated with microcytic or macrocytic anemia. Excess alcohol generally causes macrocytic anemia. (See "Diagnostic approach to anemia in adults" and "Microcytosis/Microcytic anemia".)

Indications for referral (hematologist or gastroenterologist) — Referral to a hematologist is not indicated in the majority of patients with straightforward iron deficiency. However, referral is appropriate for those in whom iron studies are inconclusive, the diagnosis is unclear, or the administration of intravenous iron is under consideration. Referral to a gastroenterologist is appropriate in individuals for whom an occult source of gastrointestinal blood loss or malabsorption is suspected.

SCREENING (ASYMPTOMATIC INDIVIDUALS)

Overview of screening considerations — In clinical research and guideline panels, a clear distinction is made between evaluation of symptoms by obtaining a complete blood count (CBC) or CBC plus iron studies in a

woman with heavy menstrual periods and fatigue, versus screening, by obtaining a CBC or iron studies in a truly asymptomatic individual.

In practice, these distinctions can blur. Symptoms can be subtle, and some patients may only become aware of symptoms in retrospect (eg, after iron deficiency or iron deficiency anemia has been recognized and treated).

For those who are asymptomatic, physicians often need to consider many factors including age, sex, menstrual and pregnancy history, gastrointestinal conditions that could affect absorption of iron, patient concerns, and family history, in determining whether it is appropriate to screen for iron deficiency or iron deficiency anemia.

Ideally, the recommendation for individuals who are truly asymptomatic would be based on high-quality evidence from randomized trials that answered the question of whether screening improved patient-important outcomes. However, trials that compare screening versus not screening otherwise healthy individuals have not been conducted and trials in which some individuals are not screened may be challenging to conduct. In the absence of randomized trials, clinicians may benefit from reviewing the prevalence of iron deficiency, availability of resources for screening, and competing needs in their specific patient population. The following may be helpful:

- All experts agree that an individual with any symptoms or physical findings suggestive of iron deficiency should be tested, as outlined above. (See 'Diagnostic evaluation' above.)

- Experts vary in their decision-making and practice regarding screening asymptomatic individuals for iron deficiency, and these decisions can be individualized according to local guidance, the patient population, individual patient factors (including other aspects of medical care that may take priority), and patient preference.

    - We do not routinely screen every adult for iron deficiency, but we do screen those at higher risk. (See 'Causes and risk factors for iron deficiency' above.)

        - We are most likely to screen those at highest risk of iron deficiency and its complications, including premenopausal women, particularly those with prior pregnancies or heavy menstrual periods, as well as individuals with conditions that might cause blood loss or iron malabsorption (see 'Blood loss' above). Screening in pregnant women is discussed separately. (See "Anemia in pregnancy".)

        - In some populations, not screening for iron deficiency is reasonable. This is especially true for men, postmenopausal women, individuals who lack risk factors for iron deficiency, individuals for whom other aspects of medical care are more pressing, and individuals who are not concerned or distressed by the possibility of not being screened. These individuals may still have a CBC for other reasons, and if a CBC is done, the results, including the mean corpuscular volume (MCV), should be reviewed. (See 'Stages of iron deficiency' above.)

    The method of screening and frequency are also individualized according to the risk profile and findings on prior testing, as discussed below. (See 'Method of screening and frequency' below.)

Practices may also shift as new information emerges regarding the prevalence and complications of iron deficiency. (See 'Epidemiology' above and "Anemia in pregnancy", section on 'Pros and cons of screening'.)

Method of screening and frequency — If a decision is made to screen for iron deficiency, the following approaches can be used:

- Start with a CBC (screen for anemia), including review of the mean corpuscular volume (MCV), which decreases as iron deficiency advances. Obtain iron studies only if anemia or microcytosis is found. This may be most reasonable for individuals with a lower risk of iron deficiency and those for whom returning for a second test would not be overly burdensome.

- Obtain a CBC and iron studies concurrently. This may be most reasonable in those with a higher risk of iron deficiency and in those for whom returning for a second test would be especially burdensome or would reduce adherence to testing.

The frequency of screening is also individualized:

- Annual screening may be reasonable for those at the highest risk, such as a menstruating woman with heavy periods.
- Less frequent, or even one-time screening, may be reasonable for other individuals, especially men and postmenopausal women.

Screening recommendations of others — The variation in practice alluded to above is reflected in available guidelines, which vary in screening approaches for different populations and often remain silent on the role of screening in older adults. Many of the available recommendations focus on populations discussed separately, as discussed in the linked topic reviews.

- The Centers for Disease Control and Prevention (CDC) in the United States has developed guidelines for screening various patient groups for iron deficiency, to detect deficiency at earlier stages and prevent serious complications of iron deficiency anemia in at-risk populations, as well as dietary recommendations to reduce the risk of iron deficiency [1,2,3]. Screening recommendations include the following:

    - Screening of adolescent and adult females of childbearing age every 5 years with a hemoglobin or hematocrit, with more frequent screening (yearly) if there is extensive menstrual blood loss, low iron intake, or a history of iron deficiency. An abnormal result is repeated, and if anemia persists, a course of iron therapy is given. Further evaluation using red blood cell (RBC) indices and serum ferritin is done if the trial of iron is ineffective. Notation is also made of the possibility of sickle cell disease or thalassemia, especially in the most frequently affected ethnic groups. (See "Iron requirements and iron deficiency in adolescents".)

    - Evaluation of the RBC indices, RBC count, and family history, so as not to miss a case of thalassemia, sickle cell disease, or other inherited condition, as stated in the guidelines.

- Recommendations for adolescents and pregnant women are discussed separately. (See "Iron requirements and iron deficiency in adolescents", section on 'Screening' and "Anemia in pregnancy", section on 'Screening during pregnancy'.)

- In contrast, 2019 guidelines from the United Kingdom recommend screening all high-risk pregnant women for iron deficiency using serum ferritin [87].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anemia in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Anemia caused by low iron (The Basics)")
- Beyond the Basics topics (see "Patient education: Anemia caused by low iron in adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Iron deficiency affects over 12 percent of the world's population, especially women, children, and individuals living in under-resourced and middle-income countries. The absolute prevalence depends on the population studied (figure 1). (See 'Epidemiology' above.)
- Major causes of iron deficiency include blood loss and reduced absorption (eg, due to celiac disease, *Helicobacter pylori*, gastritis, or bariatric surgery). Less common causes include use of erythropoiesis-stimulating agents (ESAs), urinary or pulmonary hemosiderosis, or rare inherited disorders. (See 'Causes and risk factors for iron deficiency' above.)
- Iron deficiency occurs in several stages, as illustrated by progressive changes in laboratory findings (table 4). (See 'Stages of iron deficiency' above.)
- Clinical manifestations of iron deficiency depend on severity and may include symptoms of anemia, pica, and restless legs syndrome. The examination may be normal or show pallor, alopecia, dry skin, atrophic glossitis (picture 2), angular cheilitis (picture 4), or koilonychia (spoon nails) (picture 6). The complete blood count (CBC) may be normal or show microcytic, hypochromic anemia (picture 1) with low red blood cell (RBC) and reticulocyte counts and an elevated platelet count. (See 'Clinical manifestations' above.)
- Any individual with symptoms of iron deficiency or iron deficiency anemia should be tested, either with a CBC followed by iron studies or a CBC and iron studies simultaneously. (See 'Overview of evaluation' above.)

- A number of tests are available for evaluating iron status. Iron studies can be ordered as a panel that includes iron, transferrin or total iron binding capacity (TIBC), calculated transferrin saturation (TSAT), and ferritin (algorithm 1); alternatively, an individual test can be ordered first, with additional testing if needed. Serum ferritin is the most useful, especially in uncomplicated patients such as those without a chronic inflammatory state or multifactorial anemia.

  - A serum ferritin level <30 ng/mL is considered confirmatory for iron deficiency. (See 'Diagnosis' above.)

  - More complex patients may require additional testing including TSAT, soluble transferrin receptor (sTfR) or sTfR-ferritin index, reticulocyte hemoglobin content (CHr), or bone marrow iron stain. (See 'Patients with inconclusive initial testing or comorbidities' above.)

  - A response to a therapeutic trial of iron administration may be helpful in confirming the diagnosis of iron deficiency anemia. Lack of a response may be due to an alternative diagnosis or to conditions such as celiac disease or *H. pylori* infection. (See 'Response to a therapeutic trial of iron' above and "Treatment of iron deficiency anemia in adults", section on 'Approaches to lack of response'.)

- Patients with iron deficiency or iron deficiency anemia should have a thorough history and examination for possible causes of the deficiency, which may precede the final diagnosis. Those with confirmed iron deficiency for whom a cause is not obvious should have additional evaluations that may include endoscopy as well as testing for *H. pylori*, autoimmune gastritis, and/or celiac disease, especially in individuals age 50 or older and those who do not have a response to iron repletion. (See 'Search for source of blood and iron loss' above.)

- The differential diagnosis of iron deficiency includes a number of other causes of fatigue, pica, and restless legs syndrome. The major conditions in the differential diagnosis of iron deficiency anemia include thalassemias, sideroblastic anemias, and the anemia of chronic inflammation/anemia of chronic disease. (See 'Differential diagnosis' above and "Clinical manifestations and diagnosis of the thalassemias" and "Anemia of chronic disease/anemia of inflammation".)

- The decision to screen for iron deficiency anemia or iron deficiency without anemia is individualized based on the likelihood of deficiency and its complications as well as other patient factors. (See 'Screening (asymptomatic individuals)' above.)

  - For premenopausal women (particularly those with prior pregnancies or heavy menstrual periods) and other individuals at increased risk for iron deficiency, we suggest screening (**Grade 2C**). However, not screening is also reasonable, especially if other aspects of their medical care are more pressing. (See 'Overview of screening considerations' above.)

    The most appropriate test (CBC or CBC plus iron studies) and frequency of screening are individualized. (See 'Method of screening and frequency' above.)

  - For postmenopausal women and men, we suggest not screening (**Grade 2C**). However, screening may be reasonable, and we have a low threshold for evaluating symptoms or findings that suggest possible iron deficiency or iron deficiency anemia. (See 'Clinical manifestations' above.)

- Treatment of iron deficiency and iron deficiency anemia in adults is presented in detail separately. (See "Treatment of iron deficiency anemia in adults".)

- Related topics, including an overall approach to anemia in adults and the diagnosis of iron deficiency in children, pregnant women, and individuals with chronic renal failure, are also discussed separately. (See "Diagnostic approach to anemia in adults" and "Approach to the child with anemia" and "Maternal adaptations to pregnancy: Hematologic changes" and "Diagnosis of iron deficiency in chronic kidney disease".)

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REFERENCES

1. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood 2014; 123:615.
2. http://www.cdc.gov/nchs/data/nhanes/survey_content_99_16.pdf (Accessed on June 07, 2016).
3. Centers for Disease Control and Prevention (CDC). Iron deficiency--United States, 1999-2000. MMWR Morb Mortal Wkly Rep 2002; 51:897.
4. Gupta PM, Hamner HC, Suchdev PS, et al. Iron status of toddlers, nonpregnant females, and pregnant females in the United States. Am J Clin Nutr 2017; 106:1640S.
5. Philip KEJ, Sadaka AS, Polkey MI, et al. The prevalence and associated mortality of non-anaemic iron deficiency in older adults: a 14 years observational cohort study. Br J Haematol 2020; 189:566.
6. Price EA, Mehra R, Holmes TH, Schrier SL. Anemia in older persons: etiology and evaluation. Blood Cells Mol Dis 2011; 46:159.
7. Barton JC, Wiener HH, Acton RT, et al. Prevalence of iron deficiency in 62,685 women of seven race/ethnicity groups: The HEIRS Study. PLoS One 2020; 15:e0232125.
8. Mast AE, Bialkowski W, Bryant BJ, et al. A randomized, blinded, placebo-controlled trial of education and iron supplementation for mitigation of iron deficiency in regular blood donors. Transfusion 2016; 56:1588.
9. Baart AM, van Noord PA, Vergouwe Y, et al. High prevalence of subclinical iron deficiency in whole blood donors not deferred for low hemoglobin. Transfusion 2013; 53:1670.
10. Mantilla-Gutiérrez CY, Cardona-Arias JA. [Iron deficiency prevalence in blood donors: a systematic review, 2001-2011]. Rev Esp Salud Publica 2012; 86:357.

11. Cook JD, Skikne BS. Iron deficiency: definition and diagnosis. J Intern Med 1989; 226:349.

12. Bryant BJ, Yau YY, Arceo SM, et al. Ascertainment of iron deficiency and depletion in blood donors through screening questions for pica and restless legs syndrome. Transfusion 2013; 53:1637.

13. Spencer B. Blood donor iron status: are we bleeding them dry? Curr Opin Hematol 2013; 20:533.

14. Annibale B, Capurso G, Chistolini A, et al. Gastrointestinal causes of refractory iron deficiency anemia in patients without gastrointestinal symptoms. Am J Med 2001; 111:439.

15. Camaschella C. Iron-deficiency anemia. N Engl J Med 2015; 372:1832.

16. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet 2016; 387:907.

17. Khadem G, Scott IA, Klein K. Evaluation of iron deficiency anaemia in tertiary hospital settings: room for improvement? Intern Med J 2012; 42:658.

18. Ho CH, Chau WK, Hsu HC, et al. Predictive risk factors and prevalence of malignancy in patients with iron deficiency anemia in Taiwan. Am J Hematol 2005; 78:108.

19. Ioannou GN, Rockey DC, Bryson CL, Weiss NS. Iron deficiency and gastrointestinal malignancy: a population-based cohort study. Am J Med 2002; 113:276.

20. Camaschella C. Iron deficiency: new insights into diagnosis and treatment. Hematology Am Soc Hematol Educ Program 2015; 2015:8.

21. Pawlak R, Berger J, Hines I. Iron Status of Vegetarian Adults: A Review of Literature. Am J Lifestyle Med 2018; 12:486.

22. Harper JW, Holleran SF, Ramakrishnan R, et al. Anemia in celiac disease is multifactorial in etiology. Am J Hematol 2007; 82:996.

23. Unsworth DJ, Lock FJ, Harvey RF. Iron-deficiency anaemia in premenopausal women. Lancet 1999; 353:1100.

24. Corazza GR, Valentini RA, Andreani ML, et al. Subclinical coeliac disease is a frequent cause of iron-deficiency anaemia. Scand J Gastroenterol 1995; 30:153.

25. Unsworth DJ, Lock RJ, Harvey RF. Improving the diagnosis of coeliac disease in anaemic women. Br J Haematol 2000; 111:898.

26. Hershko C, Lahad A, Kereth D. Gastropathic sideropenia. Best Pract Res Clin Haematol 2005; 18:363.

27. Kulnigg-Dabsch S, Resch M, Oberhuber G, et al. Iron deficiency workup reveals high incidence of autoimmune gastritis with parietal cell antibody as reliable screening test. Semin Hematol 2018; 55:256.

28. Hershko C, Hoffbrand AV, Keret D, et al. Role of autoimmune gastritis, Helicobacter pylori and celiac disease in refractory or unexplained iron deficiency anemia. Haematologica 2005; 90:585.

29. Tran-Duy A, Connell NJ, Vanmolkot FH, et al. Use of proton pump inhibitors and risk of iron deficiency: a population-based case-control study. J Intern Med 2019; 285:205.

30. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. Ther Adv Drug Saf 2013; 4:125.

31. Kalantar-Zadeh K, Höffken B, Wünsch H, et al. Diagnosis of iron deficiency anemia in renal failure patients during the post-erythropoietin era. Am J Kidney Dis 1995; 26:292.

32. Eschbach JW, Cook JD, Scribner BH, Finch CA. Iron balance in hemodialysis patients. Ann Intern Med 1977; 87:710.

33. Delbini P, Vaja V, Graziadei G, et al. Genetic variability of TMPRSS6 and its association with iron deficiency anaemia. Br J Haematol 2010; 151:281–4.

34. Hershko C, Camaschella C. How I treat unexplained refractory iron deficiency anemia. Blood 2014; 123:326.

35. Finberg KE, Heeney MM, Campagna DR, et al. Mutations in TMPRSS6 cause iron-refractory iron deficiency anemia (IRIDA). Nat Genet 2008; 40:569.

36. Guillem F, Lawson S, Kannengiesser C, et al. Two nonsense mutations in the TMPRSS6 gene in a patient with microcytic anemia and iron deficiency. Blood 2008; 112:2089.

37. Melis MA, Cau M, Congiu R, et al. A mutation in the TMPRSS6 gene, encoding a transmembrane serine protease that suppresses hepcidin production, in familial iron deficiency anemia refractory to oral iron. Haematologica 2008; 93:1473.

38. Edison ES, Athiyarath R, Rajasekar T, et al. A novel splice site mutation c.2278 (-1) G>C in the TMPRSS6 gene causes deletion of the substrate binding site of the serine protease resulting in refractory iron deficiency anaemia. Br J Haematol 2009; 147:766.

39. De Falco L, Sanchez M, Silvestri L, et al. Iron refractory iron deficiency anemia. Haematologica 2013; 98:845.

40. Jaspers A, Caers J, Le Gac G, et al. A novel mutation in the CUB sequence of matriptase-2 (TMPRSS6) is implicated in iron-resistant iron deficiency anaemia (IRIDA). Br J Haematol 2013; 160:564.

41. Khuong-Quang DA, Schwartzentruber J, Westerman M, et al. Iron refractory iron deficiency anemia: presentation with hyperferritinemia and response to oral iron therapy. Pediatrics 2013; 131:e620.

42. Poggiali E, Andreozzi F, Nava I, et al. The role of TMPRSS6 polymorphisms in iron deficiency anemia partially responsive to oral iron treatment. Am J Hematol 2015; 90:306.

43. Silvestri L, Guillem F, Pagani A, et al. Molecular mechanisms of the defective hepcidin inhibition in TMPRSS6 mutations associated with iron-refractory iron deficiency anemia. Blood 2009; 113:5605.

44. Heeney MM, Finberg KE. Iron-refractory iron deficiency anemia (IRIDA). Hematol Oncol Clin North Am 2014; 28:637.

45. Nai A, Pagani A, Silvestri L, Camaschella C. Increased susceptibility to iron deficiency of Tmprss6-haploinsufficient mice. Blood 2010; 116:851.

46. Finberg KE, Whittlesey RL, Fleming MD, Andrews NC. Down-regulation of Bmp/Smad signaling by Tmprss6 is required for maintenance of systemic iron homeostasis. Blood 2010; 115:3817.

47. Casu C, Rivella S. Iron age: novel targets for iron overload. Hematology Am Soc Hematol Educ Program 2014; 2014:216.

48. Stirnberg M, Gütschow M. Matriptase-2, a regulatory protease of iron homeostasis: possible substrates, cleavage sites and inhibitors. Curr Pharm Des 2013; 19:1052.

49. Mims MP, Guan Y, Pospisilova D, et al. Identification of a human mutation of DMT1 in a patient with microcytic anemia and iron overload. Blood 2005; 105:1337.

50. Iolascon A, d'Apolito M, Servedio V, et al. Microcytic anemia and hepatic iron overload in a child with compound heterozygous mutations in DMT1 (SCL11A2). Blood 2006; 107:349.

51. Beaumont C, Delaunay J, Hetet G, et al. Two new human DMT1 gene mutations in a patient with microcytic anemia, low ferritinemia, and liver iron overload. Blood 2006; 107:4168.

52. Iolascon A, De Falco L. Mutations in the gene encoding DMT1: clinical presentation and treatment. Semin Hematol 2009; 46:358.

53. Barrios M, Moreno-Carralero MI, Cuadrado-Grande N, et al. The homozygous mutation G75R in the human SLC11A2 gene leads to microcytic anaemia and iron overload. Br J Haematol 2012; 157:514.

54. Burden RJ, Pollock N, Whyte GP, et al. Effect of Intravenous Iron on Aerobic Capacity and Iron Metabolism in Elite Athletes. Med Sci Sports Exerc 2015; 47:1399.

55. Coates A, Mountjoy M, Burr J. Incidence of Iron Deficiency and Iron Deficient Anemia in Elite Runners and Triathletes. Clin J Sport Med 2017; 27:493.

56. Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. Blood 2003; 101:3359.

57. Cook JD, Finch CA, Smith NJ. Evaluation of the iron status of a population. Blood 1976; 48:449.

58. Cook JD, Skikne BS, Lynch SR, Reusser ME. Estimates of iron sufficiency in the US population. Blood 1986; 68:726.

59. Scott DE, Pritchard JA. Iron deficiency in healthy young college women. JAMA 1967; 199:897.

60. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood 2010; 116:4754.

61. Thomas DW, Hinchliffe RF, Briggs C, et al. Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol 2013; 161:639.

62. Johnson BE. Pica. In: Clinical Methods: The History, Physical, and Laboratory Examinations, 3rd edition, Walker HK, Hall WD, Hurst JW (Eds), Butterworths, Boston 1990.

63. Simpson E, Mull JD, Longley E, East J. Pica during pregnancy in low-income women born in Mexico. West J Med 2000; 173:20.

64. Kettaneh A, Eclache V, Fain O, et al. Pica and food craving in patients with iron-deficiency anemia: a case-control study in France. Am J Med 2005; 118:185.

65. Rector WG Jr. Pica: its frequency and significance in patients with iron-deficiency anemia due to chronic gastrointestinal blood loss. J Gen Intern Med 1989; 4:512.

66. Reynolds RD, Binder HJ, Miller MB, et al. Pagophagia and iron deficiency anemia. Ann Intern Med 1968; 69:435.

67. Tunnessen WW, Smith C, Oski FA. Beeturia. A sign of iron deficiency. Am J Dis Child 1969; 117:424.

68. Sotos JG. Beeturia and iron absorption. Lancet 1999; 354:1032.

69. WATSON WC, LUKE RG, INALL JA. BEETURIA: ITS INCIDENCE AND A CLUE TO ITS MECHANISM. Br Med J 1963; 2:971.

70. Allen RP, Auerbach S, Bahrain H, et al. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. Am J Hematol 2013; 88:261.

71. Allen RP, Picchietti DL, Auerbach M, et al. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Med 2018; 41:27.

72. Schieffer KM, Chuang CH, Connor J, et al. Association of Iron Deficiency Anemia With Hearing Loss in US Adults. JAMA Otolaryngol Head Neck Surg 2017; 143:350.

73. Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. Am J Hematol 2016; 91:31.

74. Osaki T, Ueta E, Arisawa K, et al. The pathophysiology of glossal pain in patients with iron deficiency and anemia. Am J Med Sci 1999; 318:324.

75. Trost LB, Bergfeld WF, Calogeras E. The diagnosis and treatment of iron deficiency and its potential relationship to hair loss. J Am Acad Dermatol 2006; 54:824.

76. HOWELL JT, MONTO RW. Syndrome of anemia, dysphagia and glossitis (Plummer Vinson syndrome). N Engl J Med 1953; 249:1009.

77. Crosby WH. Whatever became of chlorosis? JAMA 1987; 257:2799.

78. Makhoul Z, Taren D, Duncan B, et al. Risk factors associated with anemia, iron deficiency and iron deficiency anemia in rural Nepali pregnant women. Southeast Asian J Trop Med Public Health 2012; 43:735.

79. Brugnara C. Use of reticulocyte cellular indices in the diagnosis and treatment of hematological disorders. Int J Clin Lab Res 1998; 28:1.

80. Mast AE, Blinder MA, Dietzen DJ. Reticulocyte hemoglobin content. Am J Hematol 2008; 83:307.

81. Brugnara C, Zurakowski D, DiCanzio J, et al. Reticulocyte hemoglobin content to diagnose iron deficiency in children. JAMA 1999; 281:2225.

82. Fishbane S, Galgano C, Langley RC Jr, et al. Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. Kidney Int 1997; 52:217.

83. Cook JD. Clinical evaluation of iron deficiency. Semin Hematol 1982; 19:6.

84. Finch CA, Huebers H. Perspectives in iron metabolism. N Engl J Med 1982; 306:1520.

85. Tran TN, Eubanks SK, Schaffer KJ, et al. Secretion of ferritin by rat hepatoma cells and its regulation by inflammatory cytokines and iron. Blood 1997; 90:4979.

86. van den Broek NR, Letsky EA, White SA, Shenkin A. Iron status in pregnant women: which measurements are valid? Br J Haematol 1998; 103:817.

87. Pavord S, Daru J, Prasannan N, et al. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2020; 188:819.

88. Auerbach M, Abernathy J, Juul S, et al. Prevalence of iron deficiency in first trimester, nonanemic pregnant women. J Matern Fetal Neonatal Med 2021; 34:1002.

89. Lok CN, Loh TT. Regulation of transferrin function and expression: review and update. Biol Signals Recept 1998; 7:157.

90. Radtke H, Meyer T, Kalus U, et al. Rapid identification of iron deficiency in blood donors with red cell indexes provided by Advia 120. Transfusion 2005; 45:5.

91. Punnonen K, Irjala K, Rajamäki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. Blood 1997; 89:1052.

92. Brugnara C. Iron deficiency and erythropoiesis: new diagnostic approaches. Clin Chem 2003; 49:1573.

93. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005; 352:1011.

94. Suominen P, Punnonen K, Rajamäki A, Irjala K. Serum transferrin receptor and transferrin receptor-ferritin index identify healthy subjects with subclinical iron deficits. Blood 1998; 92:2934.

95. Malope BI, MacPhail AP, Alberts M, Hiss DC. The ratio of serum transferrin receptor and serum ferritin in the diagnosis of iron status. Br J Haematol 2001; 115:84.

96. Cazzola M, Beguin Y, Bergamaschi G, et al. Soluble transferrin receptor as a potential determinant of iron loading in congenital anaemias due to ineffective erythropoiesis. Br J Haematol 1999; 106:752.

97. Brugnara C, Schiller B, Moran J. Reticulocyte hemoglobin equivalent (Ret He) and assessment of iron-deficient states. Clin Lab Haematol 2006; 28:303.

98. Brittenham GM, Andersson M, Egli I, et al. Circulating non-transferrin-bound iron after oral administration of supplemental and fortification doses of iron to healthy women: a randomized study. Am J Clin Nutr 2014; 100:813.

99. Schümann K, Kroll S, Romero-Abal ME, et al. Impact of oral iron challenges on circulating non-transferrin-bound iron in healthy Guatemalan males. Ann Nutr Metab 2012; 60:98.

100. Kitsati N, Liakos D, Ermeidi E, et al. Rapid elevation of transferrin saturation and serum hepcidin concentration in hemodialysis patients after intravenous iron infusion. Haematologica 2015; 100:e80.

101. Aalto K, Honkanen V, Lahdenne P. Iron status during anti-TNF therapy in children with juvenile idiopathic arthritis. Clin Rheumatol 2011; 30:115.

102. Atkinson MA, Leonard MB, Herskovitz R, et al. Changes in Hepcidin and Hemoglobin After Anti-TNF-alpha Therapy in Children and Adolescents With Crohn Disease. J Pediatr Gastroenterol Nutr 2018; 66:90.

103. Cavallaro F, Duca L, Pisani LF, et al. Anti-TNF-Mediated Modulation of Prohepcidin Improves Iron Availability in Inflammatory Bowel Disease, in an IL-6-Mediated Fashion. Can J Gastroenterol Hepatol 2017; 2017:6843976.

104. Saxena S, Shulman IA, Johnson C. Effect of blood transfusion on serum iron and transferrin saturation. Arch Pathol Lab Med 1993; 117:622.

105. Froissart A, Rossi B, Ranque B, et al. Effect of a Red Blood Cell Transfusion on Biological Markers Used to Determine the Cause of Anemia: A Prospective Study. Am J Med 2018; 131:319.

106. Cortés-Puch I, Wang D, Sun J, et al. Washing older blood units before transfusion reduces plasma iron and improves outcomes in experimental canine pneumonia. Blood 2014; 123:1403.

107. Hod EA, Brittenham GM, Billote GB, et al. Transfusion of human volunteers with older, stored red blood cells produces extravascular hemolysis and circulating non-transferrin-bound iron. Blood 2011; 118:6675.

108. Hirano K, Morinobu T, Kim H, et al. Blood transfusion increases radical promoting non-transferrin bound iron in preterm infants. Arch Dis Child Fetal Neonatal Ed 2001; 84:F188.

109. Guyatt GH, Oxman AD, Ali M, et al. Laboratory diagnosis of iron-deficiency anemia: an overview. J Gen Intern Med 1992; 7:145.

110. Hallberg L, Bengtsson C, Lapidus L, et al. Screening for iron deficiency: an analysis based on bone-marrow examinations and serum ferritin determinations in a population sample of women. Br J Haematol

1993; 85:787.

111. Mast AE, Blinder MA, Gronowski AM, et al. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. Clin Chem 1998; 44:45.

112. Harju E, Pakarinen A, Larmi T. A comparison between serum ferritin concentration and the amount of bone marrow stainable iron. Scand J Clin Lab Invest 1984; 44:555.

113. Fairbanks VF. Laboratory testing for iron status. Hosp Pract 1990; 26:17.

114. Zanella A, Gridelli L, Berzuini A, et al. Sensitivity and predictive value of serum ferritin and free erythrocyte protoporphyrin for iron deficiency. J Lab Clin Med 1989; 113:73.

115. McMahon LF Jr, Ryan MJ, Larson D, Fisher RL. Occult gastrointestinal blood loss in marathon runners. Ann Intern Med 1984; 100:846.

116. Finch CA, Bellotti V, Stray S, et al. Plasma ferritin determination as a diagnostic tool. West J Med 1986; 145:657.

117. Brittenham GM. Disorders of iron metabolism: Iron deficiency and overload. In: Hematology Basic Princip les and Practice, 2nd ed, Hoffman R, Benz EJ Jr, Shattil SJ, et al. (Eds), Churchill Livingstone, New York 1995.

118. Bridges KR, Seligman PA. Disorders of iron metabolism. In: Blood: Principles & Practice of Hematology, Handin RI, Lux SE, Stossel TP (Eds), 1995. p.ch.49.

119. McSorley ST, Jones I, McMillan DC, Talwar D. Quantitative data on the magnitude of the systemic inflammatory response and its relationship with serum measures of iron status. Transl Res 2016; 176:119.

120. Goddard AF, James MW, McIntyre AS, et al. Guidelines for the management of iron deficiency anaemia. Gut 2011; 60:1309.

121. Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. N Engl J Med 1993; 329:1691.

122. Hreinsson JP, Jonasson JG, Bjornsson ES. Bleeding-related symptoms in colorectal cancer: a 4-year nationwide population-based study. Aliment Pharmacol Ther 2014; 39:77.

123. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998; 47:1.

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