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Iron Deficiency Anemia

Iron deficiency anemia (IDA) is caused by iron deficiency, a common yet underrecognized clinical entity. Populations at greatest risk include children, menstruating and pregnant persons, and people of low socioeconomic status. Timely diagnosis and management of iron deficiency are key to preventing IDA and require thorough assessment of the underlying cause and appropriate iron repletion through either oral or parenteral therapy. Blood transfusion does not provide adequate elemental iron but is sometimes indicated along with iron therapy in patients with cardiovascular compromise, active bleeding, or severe anemia where more rapid correction is warranted. Alternative causes of anemia can be differentiated by red blood cell morphology and reticulocyte count and should be considered if anemia persists despite adequate repletion of iron stores.

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Epidemiology, Screening, and Prevention

What is iron deficiency anemia (IDA), and what causes it?

Anemia, a reduction in red blood cell (RBC) mass and/or hemoglobin (Hgb) concentration, is defined by the World Health Organization (WHO) as an Hgb level below 12.0 g/dL in females and below 13.0 g/dL in males (1), although evidence supporting sex-specific Hgb thresholds has been questioned (2, 3). Approximately 1.92 billion prevalent cases of anemia are estimated worldwide (4). Although the underlying pathophysiology of anemia is diverse, iron deficiency (ID) is the leading cause of anemia and is designated by WHO as 1 of the 10 most important contributors to the global burden of disease (5).

ID can be defined as "absolute" or "functional." Absolute ID refers to a severe reduction or absence of iron stores, whereas functional ID results from insufficient iron availability in the presence of adequate stores. Functional ID is most commonly seen in settings of chronic disease and inflammation, whereby cytokines induce hepcidin production and macrophage sequestration of iron, suppressing erythropoietic response (6).

The balance of iron in the body is maintained through sophisticated regulatory mechanisms. Because the body has no mechanism for active iron excretion, absorption of iron is tightly controlled at the level of dietary uptake in the gut (6). Absolute ID can develop via 3 primary mechanisms: 1) chronic or excessive blood loss in the setting of heavy menstrual bleeding (HMB), gastrointestinal (GI) bleeding, or frequent blood donation; 2) increased demands in the setting of childhood growth or pregnancy; or 3) insufficient dietary intake or malabsorption.

How common are ID and IDA, and who is at risk?

The precise definition of ID varies, but data from the 2017–2020 National Health and Nutrition Examination Survey suggest that absolute ID (defined as ferritin level <30 μg/L) affects 14% of U.S. adults and functional ID (defined as ferritin level ≥30 μg/L with transferrin saturation [Tsat] <20%) affects 15% of U.S. adults (7). Risk factors for ID are summarized in the **Box:** Risk Factors for Iron Deficiency. People of childbearing potential are at greater risk due to obligate iron losses through menstruation and fetal and RBC growth demands during pregnancy (8, 9). The WHO estimates that 37% of pregnant persons and 30% of reproductive-aged biological females aged 15 to 49 years are affected by anemia (10). The overall prevalence of ID in U.S. nonpregnant females aged 12 to 21 years is estimated at 39% based on a serum ferritin cutoff of less than 15 μg/L and 78% when a cutoff of 50 μg/L is used (8).

HMB, defined as menstrual blood loss of more than 80 mL per cycle, is the leading contributor to ID among reproductive-aged persons from high-income countries and can lead to loss of more than 40 mg of iron per menstrual cycle (9). HMB is often underappreciated by both patients and health care providers, in part due to historical and cultural stigma associated with discussion of menstruation and normalization of bleeding symptoms (11).

People of low socioeconomic status (SES) are at higher risk for ID due to reduced intake of and access to iron-rich foods and decreased access to health care (12). This is particularly apparent in pregnancy, where multiple studies have found that those of lower SES were also less likely to undergo routine ferritin screening in pregnancy and less likely to receive iron supplementation compared with those of higher SES (9, 13).

GI bleeding is another common source of ID, especially in males and postmenopausal females. GI cancer is the most serious potential cause of bleeding, although peptic ulcer disease, inflammatory bowel disease (IBD), and other GI lesions such as colonic polyps and angiodysplasia can also contribute.

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Risk Factors for Iron Deficiency

Insufficient iron uptake:

- Insufficient dietary iron content: Vegan/vegetarian diet, malnutrition, food insecurity, excessive milk intake.
- Inadequate absorption: Bariatric surgery, celiac disease, *H pylori*, IBD, atrophic gastritis, proton-pump inhibitors/H_2 blockers.

Increased iron requirements: Growth (infancy, adolescence), pregnancy, ESAs.

Acute and chronic blood loss: GI bleeding (peptic ulcer disease, arteriovenous malformations, neoplasms, IBD), gynecologic bleeding (menstrual losses, fibroids), urinary blood loss, regular blood donation, bleeding disorders, anticoagulant/antiplatelet use, high-intensity athletic activity.

Functional causes: Congestive HF, CKD, IBD, other chronic inflammatory conditions.

In a cross-sectional study across 16 hospitals in the Netherlands, the prevalence of anemia and ID among 2197 patients with IBD was estimated at 18% and 43%, respectively (14). Females were at least 2 times as likely as males to have ID (odds ratio, 2.63 [95% CI, 1.84 to 3.75]). However, 41% of anemia cases could not be characterized, which is a major limitation.

Antiplatelet and anticoagulant use can also potentiate bleeding symptoms, resulting in recurrent ID. Aspirin and other nonsteroidal anti-inflammatory agents predispose people to gastric ulcers and erosions, increasing the risk for occult GI bleeding and exacerbating menstrual blood loss. HMB is estimated to affect more than 60% of menstruating persons receiving anticoagulation and is increasingly recognized in those using antiplatelets (15).

Impaired dietary absorption is another important cause of ID. The primary site of absorption of iron is in the proximal duodenum and requires the conversion of ferric (Fe^{3+}) to ferrous (Fe^{2+}) iron for uptake. *Helicobacter pylori* infection contributes to peptic ulcer disease but can also result in achlorhydria and the development of autoimmune gastritis, further impairing iron absorption (16). People with celiac disease can also present with ID from impaired absorption due to villous blunting and chronic GI blood loss (17). Finally, ID after bariatric surgery is highly prevalent, owing to impaired absorption, decreased tolerance of iron-rich foods, and occult GI bleeding caused by anastomotic ulcers (18).

Athletes are another group at high risk for ID from inadequate intake, chronic occult GI bleeding from severe reductions of splanchnic blood flow leading to GI ischemia and epithelial barrier dysfunction, iron losses through sweat, and elevated hepcidin levels from training-induced inflammation (19). March hemoglobinuria, another proposed mechanism, refers to traumatic intravascular hemolysis in the setting of repetitive foot strike with running or other repetitive muscle contractions (20).

In addition to the aforementioned causes, functional ID can occur in the setting of chronic inflammation leading to elevated hepcidin levels, thereby limiting iron availability. This phenomenon is commonly seen among people with chronic kidney disease (CKD) and heart failure (HF) and can be exacerbated by concurrent administration of erythropoiesis-stimulating agents (ESAs) (21).

What is the role of screening in asymptomatic patients, and what tests should be used?

Guidelines vary in the recommended target population and frequency of screening for ID. In adolescents and adults of menstruating potential, the Centers for Disease Control and Prevention (CDC) recommends screening for ID at least every 5 years, with annual screening in those with HMB, low iron intake, or history of ID (22). Although many guidelines exist on the management of ID and IDA in HMB, consensus on routine screening is lacking (23). In addition, the European Hematology

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Association (EHA) recommends systematic screening for ID in persons preparing for major surgery given their higher risk for requiring perioperative blood transfusion (24).

Despite the high prevalence of ID in pregnancy, the U.S. Preventive Services Task Force (USPSTF) recently concluded that there was insufficient evidence to support routine screening for ID in asymptomatic pregnant people (25). This contrasts with guidelines from the International Federation of Gynecology and Obstetrics (FIGO), the EHA, and U.K. guidelines, which recommend routine screening with serum ferritin in pregnancy (24, 26, 27). Another challenge is the widespread misperception that anemia is a sensitive indicator of ID. Many guidelines, including those from the American College of Obstetricians and Gynecologists, recommend routine complete blood count (CBC) tests in pregnancy without mention of serum ferritin (28). Because anemia reflects the final stage of ID, monitoring CBC alone can delay diagnosis.

How can ID and IDA be prevented?

IDA can be prevented through early recognition of low iron stores and mitigation of risk factors that perpetuate ongoing ID. In addition to screening high-risk populations, conducting a detailed history to identify populations at risk for ongoing blood loss and inadequate iron intake and absorption is key to addressing the underlying cause.

Biofortification of food and oral iron supplementation have been proposed to prevent ID in several countries and for target populations, including children and premenopausal people, especially in low- and middle-income countries (29). In the United States and many other countries, wheat and other flours and infant formulas are routinely fortified with iron. The National Institutes of Health has published recommendations for daily intake of iron stratified by age, biological sex, and pregnancy status (30). Dietary supplements of iron in the form of iron salts may benefit certain populations at risk for low dietary intake, such as those following vegetarian or vegan diets, although evidence supporting the benefit of routine iron supplementation is limited (30).

Epidemiology, Screening, and Prevention... ID is exceedingly common, especially among children, menstruating and pregnant people, and those of low SES. Absolute ID can develop through insufficient dietary intake or malabsorption, increased demands in the setting of childhood growth or pregnancy, or chronic or excessive bleeding. Early identification of ID and routine fortification of foods with iron are important preventive strategies, although guidelines vary with regard to whether and in whom routine screening should be done.

CLINICAL BOTTOM LINE

Diagnosis and Evaluation

What are common signs and symptoms of ID and IDA?

Signs and symptoms of ID can arise from subsequent anemia or from ID itself as a result of iron being diverted from other essential tissues to maintain Hgb and adequate RBC production. Common symptoms of ID with or without anemia include fatigue, lethargy, weakness, cold intolerance, and decreased exercise capacity (30). Impaired mental functioning, including reduced concentration, decreased cognition, and impaired work performance, has been described (31). Two additional classic associations of ID include pica, which refers to unusual cravings for substances that are not food sources (such as ice, soil, and paper products), and

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restless leg syndrome, with symptoms often manifesting at night (32).

Symptoms are often more severe in patients with IDA, manifesting as shortness of breath, palpitations, dizziness, tachycardia, cardiac flow murmur, or even hemodynamic instability in severe cases. Other findings include pallor, atrophic skin, koilonychia (spoon nails), hair loss, angular cheilitis, and atrophic glossitis (33). IDA in pregnancy is associated with myriad maternal and fetal complications, including preterm labor, preterm birth, placental abruption, preeclampsia, postpartum hemorrhage, postpartum depression, and even maternal death (34).

What are other common causes of anemia?

Although ID is the most common cause of anemia, it is essential to recognize and assess for alternate causes (**Table 1**). IDA typically presents with microcytosis and hypochromia, but early IDA can present as a normocytic anemia. The percentage of IDA cases that present as normocytic varies by population and clinical context, but a recent retrospective analysis of pregnant people with ID found that 59% had neither anemia nor microcytosis (35). Other major causes of microcytic anemia include thalassemia, sideroblastic anemia, and anemia of chronic disease or inflammation (36). Other

Table 1. **Differential Diagnosis of Anemia**

Differential	*Distinguishing Signs/Symptoms*	*Common Causes*
Microcytic MCV		
Iron deficiency	Low ferritin level, pica, restless legs syndrome, koilonychia, angular cheilitis, atrophic glossitis	Bleeding, decreased absorption, increased demands (growth, pregnancy)
Thalassemia	Microcytosis with high RBC count, family history, extramedullary hematopoiesis	Decreased globin chain production
Sideroblastic anemia	Basophilic stippling	Copper deficiency, MDS, inherited, medications/alcohol
ACD	Elevated ferritin level, chronic disease	Kidney disease, heart failure, IBD
Normocytic MCV		
Hemolysis	Positive DAT result; elevated reticulocyte count, LDH level, and indirect bilirubin level; low haptoglobin level	Immune and nonimmune causes (e.g., membranopathies, enzymopathies, PNH)
ACD	Elevated ferritin level, chronic disease	Kidney disease, heart failure, IBD
Chronic kidney disease	Low EPO level, elevated creatinine level, dialysis	Chronic kidney disease
Cancer	Cytopenias, positive result on SPEP, other cancer diagnosis	Hematologic cancer and malignant solid tumors
Other	NA	Early iron deficiency, infection, infiltrative, endocrine, medications, pure red cell aplasia
Macrocytic MCV		
Megaloblastic anemia	Nuclear cytoplasmic asynchrony	Vitamin B_{12}, folate, or copper deficiency; MDS; medications
Hypothyroidism	Low TSH level	Hypothyroidism
Liver disease/alcohol use disorder	Splenomegaly, thrombocytopenia	Liver disease/alcohol use disorder
Reticulocytosis	Elevated reticulocyte count	Bleeding, hemolysis, bone marrow recovery

ACD = anemia of chronic disease; DAT = direct antiglobulin test; EPO = erythropoietin; IBD = inflammatory bowel disease; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; MDS = myelodysplastic syndrome; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SPEP = serum protein electrophoresis; TSH = thyroid-stimulating hormone.

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causes of normocytic anemia include anemia of CKD, infection, hemolysis from immune and nonimmune disorders, bone marrow infiltration, and cancer.

Macrocytic anemia can be associated with megaloblastic causes due to impaired nucleic acid metabolism, generally due to deficiencies in vitamin B_{12}, folate, or copper, or medications that interfere with DNA synthesis. Other causes of megaloblastic anemia include primary bone marrow disorders (myelodysplastic syndrome), alcohol use disorder, liver disease, hypothyroidism, or increased reticulocytosis, which can be seen in hemolytic anemia or recovery from bleeding.

What are the initial laboratory tests in the evaluation of anemia?

Laboratory testing should be part of the initial evaluation for anemia and should include a CBC with differential, reticulocyte count, and review of the peripheral blood smear to further differentiate other causes of anemia based on morphology and the proliferation index (**Figure**). The CBC with differential is useful to evaluate for other cytopenias and delineate the mean corpuscular volume (MCV). Reticulocytes represent the first anucleate RBC and provide a useful estimate of RBC production to distinguish between hyperproliferative and hypoproliferative causes of anemia.

Elevations in absolute reticulocyte count should trigger evaluation of hemolysis with bilirubin, lactate dehydrogenase, haptoglobin, and a direct antiglobulin test. A hypoproliferative reticulocyte count can be further distinguished by the MCV (**Table 1**). If microcytosis (MCV <80 fL) is present, evaluation with serum ferritin or iron studies and Hgb electrophoresis is warranted to assess for ID and thalassemia, respectively. Evaluation for macrocytic anemia should include serum vitamin B_{12} and folate as well as measurement of biochemical intermediates (methylmalonic acid and homocysteine). A thyroid-stimulating hormone test; a chemistry panel, including liver function tests; copper measurement; and viral studies, including hepatitis and HIV testing, can also be considered.

Ultimately, a detailed medical history, including comorbidities, medications, recreational substances, and family history, is essential to guide further diagnostic testing.

How are IDA and ID diagnosed?

There is widespread debate about the sex-specific WHO definition of anemia (Hgb level <12.0 g/dL in females and <13.0 g/dL in males) (37), which was derived in 1968 using the fifth percentile of Hgb concentrations from a small number of studies (38–41). A major limitation of these proposed reference ranges was their derivation from a demographically narrow sample, consisting primarily of White people from high-income countries in North America and Europe. These studies did not systematically evaluate or exclude those with ID; in fact, one study reported that females receiving iron supplementation had improvements in Hgb levels (39), suggesting that sex-specific Hgb thresholds are not based on physiology but rather reflect unrecognized and untreated ID in females. The WHO has identified a key research priority of updating definitions of anemia to more accurately reflect Hgb reference ranges that are globally applicable (42).

The gold standard for diagnosing ID is iron staining of the bone marrow, but this is rarely done in practice. Instead, measurement of serum ferritin, a blood protein that contains iron, is the preferred (43) and the most sensitive and specific noninvasive diagnostic test. It reflects total body iron stores, with a ferritin level of 1 μg/L correlating with 8 mg of storage iron (44). However, interpretation of ferritin in people with underlying chronic inflammatory conditions is limited as ferritin levels may be falsely elevated. Nonetheless, because ferritin protein synthesis depends on the presence of cellular iron, an absolute lack of iron blunts elevations in serum ferritin level above 100 μg/L (45). When functional ID is suspected, ferritin in conjunction with Tsat, which refers to the percentage of transferrin (the main iron transport protein) bound to iron, may help confirm the diagnosis.

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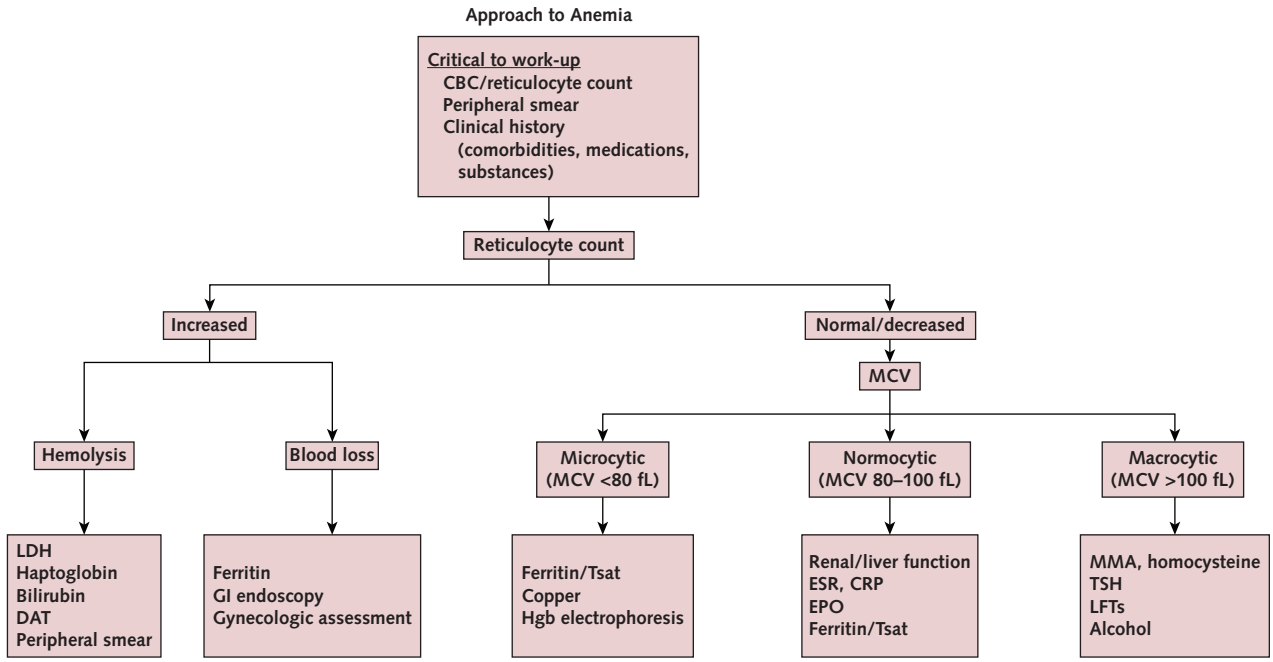
Figure. **Initial approach to the work-up of anemia.**



CBC = complete blood count; CRP = C-reactive protein; DAT = direct antiglobulin test; EPO = erythropoietin; ESR = erythrocyte sedimentation rate; GI = gastrointestinal; Hgb = hemoglobin; LDH = lactate dehydrogenase; LFT = liver function test; MCV = mean corpuscular volume; MMA = methylmalonic acid; Tsat = transferrin saturation; TSH = thyroid-stimulating hormone.

Alternate iron indices also have limitations. Serum iron levels can fluctuate due to dietary intake and supplementation and normal diurnal variation (45). Total iron-binding capacity (TIBC) indirectly estimates transferrin concentration by measuring the maximum amount of iron bound by transferrin. TIBC is typically elevated in ID but is not sensitive and can decrease in the setting of inflammation, aging, and malnutrition (45). Tsat (≤20%) is low in both ID and anemia of chronic inflammation and reflects a reduced amount of circulating iron available for erythropoiesis, limiting its utility as a standalone marker. Soluble transferrin receptor is a direct measure of tissue iron demands and serves as a biomarker of erythropoiesis not affected by inflammation (46); however, scarce availability and nonstandardized thresholds are major limitations. Reticulocyte Hgb content allows for real-time assessment of iron availability for erythropoiesis because reticulocytes are the first anucleate RBC and persist in the blood for 1 to 2 days. This marker is low in settings of iron-deficient erythropoiesis and has advantages in that it is not affected by inflammation; however, it cannot reliably distinguish between anemia from ID and chronic inflammation and may also be low in people with thalassemia (47).

The optimal threshold to diagnose ID by ferritin varies widely (3). Although a ferritin threshold of less than 15 μg/L is 98% specific, sensitivity is poor at 75% compared with bone marrow assessment of iron stores (48). The 2024 American Gastroenterological Association (AGA) guidelines use a ferritin cutoff of less than 45 μg/L (sensitivity of 85% and specificity of 92%) (49). Higher thresholds (for example, ferritin level <50 μg/L) have also been supported by physiologic studies of iron absorption (50) and have been shown to produce clinical improvement in fatigue as a repletion target (51, 52).

Alternate diagnostic thresholds for ID exist for certain patient populations. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend diagnostic criteria of a Tsat of 20% or less and ferritin level of 500 μg/L or less in patients with CKD (53). In

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patients with New York Heart Association class II or III HF with an ejection fraction of 45% or less, the 2022 American College of Cardiology/American Heart Association (ACC/AHA) Joint Committee recommends a ferritin level below 100 μg/L or a ferritin level of 100 to 299 μg/L with a Tsat below 20% to diagnose ID (54).

What other testing and evaluation should be done once a diagnosis of IDA and ID is made?

Diagnosis of IDA and ID should always be accompanied by assessment for an underlying cause. A detailed clinical history, including a thorough assessment of potential sources of bleeding, history of blood donation, and/or prior bariatric or bowel resection surgery, is critical. In males and postmenopausal females aged 45 years or older with IDA, the AGA strongly recommends upper and lower endoscopy (55). In asymptomatic premenopausal females without other obvious causes of IDA, such as HMB or pregnancy, the panel suggests endoscopic evaluation but acknowledges that the yield is likely to be lower in younger patients. If endoscopy does not reveal a culprit lesion in asymptomatic people, additional evaluation for *H pylori* is suggested, in addition to serologic testing for celiac disease in those in whom it may be plausible. Routine small bowel evaluation, including capsule endoscopy, is generally not recommended unless it is expected to change management. Finally, ID should only be attributed to diet, medications, or exercise after evaluation of alternate causes is effectively ruled out.

When should patients be hospitalized for determination of the cause of IDA?

Hospitalization for expedited work-up can be considered in patients with acute and severe anemia (Hgb level <7 to 8 g/dL) and in those with symptoms suggestive of impaired oxygen delivery. Rapid consultation with a hematologist, a gastroenterologist, and/or a gynecologist may be indicated to facilitate prompt diagnosis with targeted examination, additional laboratory work-up, endoscopy, and/or pertinent imaging studies, such as angiography.

When should clinicians suspect other causes of anemia in patients with IDA?

Alternate or concurrent causes of anemia should be suspected in patients with persistent anemia despite adequate iron repletion. Adequate repletion can be confirmed when the ferritin level exceeds 100 μg/L and the Tsat exceeds 20% (45). Additional evaluation for alternate causes of anemia (Table 1) is warranted if they have not previously been excluded.

When should patients be referred for diagnosis, and to which specialists?

ID is exceedingly common and can be managed in the primary care setting in most cases. Referral to a hematologist is appropriate for patients in whom iron studies are inconclusive or the diagnosis is unclear. Referral to a gastroenterologist or a gynecologist should be considered early to facilitate an evaluation for underlying causes of ID given the high likelihood of recurrence if the source of iron loss is not addressed.

Diagnosis and Evaluation... Ferritin measurement is the most sensitive and specific noninvasive test for assessing total body iron stores and should be used to confirm the diagnosis of ID. Because iron is stripped from enzymes and other tissues to maintain erythropoiesis, functional deficiency and fatigue can result even before progression to overt anemia. Alternate causes of anemia can be differentiated by morphology, MCV, and reticulocyte count and should be considered if anemia persists despite adequate repletion of iron stores. Consensus is lacking for a universal threshold for diagnosis of ID, although there are data to support a threshold of a ferritin level below 50 μg/L or below 100 μg/L in the setting of chronic disease or inflammation. Although ID is commonly managed in the outpatient setting, signs and symptoms of hemodynamic instability, symptomatic cardiac disease, or brisk bleeding should prompt hospitalization for expedited work-up.

CLINICAL BOTTOM LINE

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55. Ko CW, Siddique SM, Patel A, et al. AGA clinical practice guidelines on the gastrointestinal evaluation of iron deficiency anemia. Gastroenterology. 2020;159:1085-1094. [PMID: 32810434]

What are the goals of management and treatment of IDA and ID?

The goal of treatment is to correct or prevent anemia and to adequately replete deficient stores to improve symptoms and prevent recurrence. The rapidity of correction depends on the degree of symptoms, the severity of anemia, and the clinical urgency of correction, including during pregnancy, before surgery, or when iron losses rapidly outpace supply and intake.

What dietary and behavioral changes are recommended in the management of IDA?

Dietary iron is absorbed in 2 forms: nonheme iron and heme-bound iron. Nonheme iron exists primarily in the ferric (Fe^{3+}) form and requires reduction through gastric acid secretion to the ferrous (Fe^{2+}) form for optimized absorption (6). Meat, poultry, and fish are sources of heme-bound iron, whereas plant-based foods primarily contain nonheme iron and are therefore absorbed less efficiently and effectively. Dietary or other behavioral modifications, such as use of iron patches or sprays, are not recommended by themselves to treat ID and IDA. Although increasing dietary intake of iron-rich foods and other behavioral strategies such as using cast iron cookware can be valuable, they are insufficient as they do not deliver the necessary amount of elemental iron (typically 60 to 110 mg) required to effectively restore deficient total body iron stores (56).

What are different forms of nondietary iron supplementation?

Nondietary iron repletion can be achieved through iron therapy, including oral and parenteral (intravenous [IV]) iron formulations or via RBC transfusion in severe cases. **Table 2** summarizes important considerations when choosing from among available therapies.

Oral therapy

Oral iron supplementation is typically considered to be first-line treatment in uncomplicated cases of ID and IDA. Many formulations are available, including iron salts (ferrous sulfate, gluconate, fumarate), polysaccharide-iron complex, and heme iron polypeptide, without evidence to suggest superiority of any specific formulation (57). Exceptions include formulations marketed as slow-release and enteric-coated, which have reduced efficacy due to delayed liberation of encapsulated iron past the primary site of absorption in the duodenum and the upper jejunum (58).

Although both total iron and elemental iron are reported, only elemental iron is absorbed and should be the main consideration when selecting an appropriate dose. Ferrous salts are the most common and inexpensive formulation; their use is predominantly limited by GI adverse effects (**Table 2**), which correlate more closely with the dose of elemental iron rather than the specific formulation.

A randomized controlled trial (RCT) (n = 62) of the efficacy and safety of twice-daily dosing with 60 mg of ferrous sulfate compared with alternate-day dosing with 120 mg for 6 weeks found that a significantly higher proportion of participants in the twice-daily dosing group improved Hgb response (≥2-g/dL increase) at 3 weeks (32.3% vs. 6.5%; P < 0.0001) and 6 weeks (58% vs. 35.5%; P = 0.001) compared with alternate-day dosing (59). However, an Hgb increase at 3 weeks with twice-daily dosing (1.6 ± 1.2 g/dL) did not significantly differ from alternate-day dosing at 6 weeks (2.0 ± 1.3 g/dL); participants in the twice-daily dosing group also reported more adverse effects (38.7% vs. 22.5%; P = 0.03). These results suggest that twice-daily dosing for 3 weeks provided the same level of iron repletion as alternate-day dosing for 6 weeks, but at the expense of more GI adverse effects.

Similarly, an RCT (n = 150) of daily 100-mg iron for 3 months followed by placebo for 3 months compared with alternate-day iron, 100 mg, for 6 months

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Table 2. **Replacement Therapies for Iron Deficiency**

Therapy	*Indication*	*Formulation and Dosing*	*Adverse Effects*	*Other Considerations*
Oral iron	First-line treatment for uncomplicated iron deficiency (i.e., unimpaired absorption)	Ferrous sulfate, gluconate, fumarate (elemental iron) • 60–110 mg elemental iron daily • Alternate-day dosing can be considered to reduce GI adverse effects (avoid multiple doses per day)	GI: Dyspepsia, constipation, nausea, diarrhea, black stools Metallic taste Stained tooth enamel (certain liquid formulations)	Avoid agents that may inhibit absorption (calcium, phytates, tannins, PPIs/H_2 blockers) Enteric-coated or timed-release formulations are less effective and generally more expensive Reassess tolerability, adherence, and ferritin level after 4–12 weeks and switch to IV iron if inadequate response or intolerance
IV iron	Inadequate response to or intolerance of oral iron Rapid correction required (chronic or rapid blood loss, preoperative period, second or third trimester of pregnancy) Malabsorption (gastric bypass, IBD, celiac disease) CKD with Tsat ≤20% and ferritin level ≤500 μg/L HFrEF with EF ≤45% and ferritin level <100 μg/L or ferritin level of 100–299 μg/L with Tsat <20%	Iron dextran (INFeD [AbbVie]): 1000 mg × 1 dose Iron sucrose (Venofer [American Regent]): 200 mg × 5 doses Ferrous gluconate (Ferrlecit [Sanofi-Aventis]): 125–250 mg × 5 doses Ferumoxytol (Feraheme [AMAG Pharmaceuticals]): 510 mg × 2 doses Ferric carboxymaltose (Injectafer [Daiichi Sankyo]): 750 mg × 2 doses Ferric derisomaltose (Monoferric [Pharmacosmos Therapeutics]): 1000 mg × 1 dose	Infusion reaction: Mild (flushing, urticaria, pruritus, chest tightness, back pain), moderate (shortness of breath, hypotension, tachycardia), or severe (<1:200 000) (anaphylaxis, angioedema, hemodynamic instability) Hypophosphatemia with ferric carboxymaltose Metallic taste Transient headache, myalgia/arthralgia after infusion	Formulations similarly effective; selection based on availability, accessibility, cost Prioritize single-dose infusions (less burdensome, better cost-effectiveness/completion rate) Consider switching to alternate IV iron formulation if prior infusion reaction Premedication not routinely recommended; consider premedication and slower infusion rate if multiple drug allergies or history of inflammatory arthritis
Blood transfusion	Hgb level <7 g/dL (or <8 g/dL if CV conditions) Active, substantial blood loss CV compromise (angina, heart failure) and/or hemodynamic instability	Use restrictive thresholds, transfuse 1 unit of packed red blood cells at a time based on clinical judgment	Transfusion-associated circulatory overload, acute lung injury Infection transmission Allergic reaction (urticaria, anaphylaxis) Iron overload Alloimmunization Acute and delayed hemolytic transfusion reaction	Concurrent IV iron to fuel erythropoiesis (blood transfusion unlikely to fully correct iron deficit) Adhere to blood transfusion guidelines (to conserve blood products)

CKD = chronic kidney disease; CV = cardiovascular; EF = ejection fraction; GI = gastrointestinal; HFrEF = heart failure with reduced ejection fraction; Hgb = hemoglobin; IBD = inflammatory bowel disease; IV = intravenous; PPI = proton-pump inhibitor; Tsat = transferrin saturation.

demonstrated greater Hgb and ferritin responses with daily compared with alternate-day dosing at 3 months (14.0 vs. 13.7 g/dL [P < 0.05] and 43.8 vs. 31.3 μg/L [P < 0.05], respectively) (60). However, Hgb response at 6 months was similar between groups (13.4 vs. 13.4 g/dL). Nonetheless, GI toxicity was greater in the daily dosing group (prevalence ratio, 1.91 [CI, 1.71 to 2.13]; P < 0.0001).

Thus, when balancing efficacy, safety, and severity of IDA, elemental iron, 60 to 110 mg taken daily, is recommended (61). In patients who have GI adverse effects, alternate-day dosing is recommended unless rapid repletion of iron stores is indicated.

Iron absorption can be inhibited by divalent cations like calcium and magnesium, phytates (found in seeds and grains), and tannins (found in tea and coffee); these foods and beverages should not be consumed concurrently with iron (6). Certain medications, such as proton-pump inhibitors, antacids, and

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histamine receptor blockers, reduce iron absorption due to decreased gastric acidity, which impairs the conversion of ferric to ferrous iron (62). Vitamin C has been shown to increase absorption of iron, although consistent benefit and clinical relevance have not been demonstrated (63). Some evidence supports increased absorption with ingestion of heme-bound iron sources (meat, poultry, and fish) (64).

Response to oral iron therapy should be assessed to ensure adequate repletion. Pooled data from 5 RCTs suggest that an increase in Hgb level of 1.0 g/dL or greater after 2 weeks of oral iron therapy most accurately predicts satisfactory response (65).

IV therapy

IV iron is indicated for patients who do not achieve an adequate response after 12 weeks of oral iron, are intolerant of or unlikely to respond to oral iron, or require more rapid iron repletion (66), such as during the second and third trimesters of pregnancy (67), in perioperative settings (68), and when oral iron absorption is unlikely to keep up with chronic or rapid blood loss. IV iron is also preferred in patients with conditions that impair GI absorption (IBD, celiac disease, and gastric bypass surgery) (69, 70).

In addition, IV iron is considered first-line treatment for IDA in chronic diseases, such as CKD and HF with reduced ejection fraction (HFrEF), based on RCTs showing improved outcomes with IV iron and the ineffectiveness of oral iron in these populations (71, 72). In patients with CKD and IDA, KDIGO guidelines recommend iron replacement targeted to a Tsat of 20% or greater and a ferritin level of 100 μg/L or higher before consideration of initiation of ESAs, given that ESAs stimulate erythropoiesis and may worsen IDA if it is present (21). Guidelines from the ACC/AHA Joint Committee recommend IV iron in patients with HFrEF and ID (defined as ferritin level <100 μg/L or ferritin level of 100 to 299 μg/L with Tsat <20%), even in the absence of anemia (54).

Several RCTs have assessed outcomes of IV iron in patients with ID and HFrEF, with conflicting results.

*The 2020 AFFIRM-AHF trial (*n = *1132) found a significant reduction in HF hospitalizations in patients hospitalized for acute HF and ID (defined as ferritin level <100 μg/L, or ferritin level of 100 to 299 μg/L with Tsat <20%) who received IV iron versus placebo (risk ratio, 0.74 [CI, 0.58 to 0.94];* P = *0.013). There was no difference in cardiovascular death between the groups (14% vs. 14%; hazard ratio [HR], 0.96 [CI, 0.70 to 1.32];* P = *0.81) (73).*

*In contrast, a recently published RCT (*n = *1105) failed to demonstrate significant differences between IV iron and placebo in all-cause hospitalizations (rate ratio, 0.80 [CI, 0.60 to 1.06];* P = *0.12), time to first HF hospitalization, or cardiovascular death (HR, 0.79 [CI, 0.61 to 1.02];* P = *0.07) in stable outpatients with chronic HFrEF and ID (74). The study may have been underpowered as the point estimates for hospitalizations were not dissimilar to those in AFFIRM-AHF, although CIs were wider. Other limitations included a high rate of treatment discontinuation in the IV iron group (34%) and potential inadequate iron repletion.*

Although several formulations of IV iron exist, no data suggest superior efficacy and safety of one formulation over another, with the exception of IV ferric carboxymaltose, which has been associated with high rates of severe hypophosphatemia and should be avoided in patients at risk for hypophosphatemia and those requiring multiple IV infusions (75). Decision making typically relies on what is available, accessible, and affordable at the individual treatment center. A patient's total body iron deficit can be calculated using the Ganzoni equation (total iron dose = [actual body weight × (15 − actual Hgb level)] × 2.4 + iron stores). Data from clinical trials suggest

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that the average iron deficit estimated by the Ganzoni equation is approximately 1500 mg (76). Although dosing based on total iron deficit resulted in faster and greater recovery of Hgb compared with fixed-dose 1000-mg repletion, subsequent studies have shown noninferiority of treating with 1000 mg initially and reassessing iron stores at 4 to 6 weeks (77). When available, single total-dose infusions of IV iron are preferred over multiple-dose treatment due to faster time to repletion and reduced patient burden.

Safety of IV iron was historically a concern due to now-obsolete formulations of high-molecular-weight iron dextran, which were associated with unacceptably high rates of allergic and hypersensitivity reactions (78). However, a number of observational studies have found exceedingly low rates of major iron infusion reactions and anaphylaxis (<1 in 200 000) (79). Routine premedication does not meaningfully reduce infusion-related reactions and may cause adverse effects (78). Data guiding specific management strategies in patients with multiple drug allergies or a history of infusion reaction are lacking, although premedication with corticosteroids and/or switching to an alternate formulation can be considered based on low-level evidence from large cohort studies and a consensus report (80).

When should blood transfusion be considered, and how should it be done?

The American Society of Hematology and the American Association of Blood Banks Choosing Wisely campaign recommend iron repletion over RBC transfusion in hemodynamically stable, nonbleeding patients with IDA because RBC transfusion does not address the underlying ID and carries risks without added benefit in stable patients (81, 82). One RBC unit, while transiently improving Hgb, contains only 200 to 250 mg of elemental iron, which inadequately repletes iron stores in people with ID. However, in those with cardiovascular compromise, active bleeding, and/or severe anemia (Hgb level <7 or <8 g/dL), RBC transfusion should be considered, often in conjunction with IV iron infusion.

The MINT trial randomly assigned 3506 patients with myocardial infarction (MI) and Hgb level less than 10 g/dL to a restrictive transfusion strategy (Hgb threshold <7 to 8 g/dL) versus a liberal strategy (Hgb threshold <10 g/dL) (83). At 30 days, there was no significant difference in death, MI, coronary revascularization, or hospitalization between the restrictive and liberal groups (19.6% vs. 17.4%; risk ratio, 1.13 [CI, 0.98 to 1.29]), although key limitations included short follow-up, open-label design, and limited power. However, the restrictive strategy decreased blood use by 50%.

On the basis of MINT and other RCTs (83–85), the RBC transfusion threshold in most patients is an Hgb level less than 7 g/dL, or less than 8 g/dL in those with major cardiovascular comorbidities. Iron status should be assessed in all patients with anemia, and iron repletion should be administered in those meeting criteria for ID to fuel self-driven erythropoiesis.

What are risks of blood transfusion, and how can they be managed?

Risks of RBC transfusions include transfusion-associated circulatory overload, transfusion-related acute lung injury, and transmission of infection leading to sepsis. Allergic reactions, hives, and (rarely) anaphylaxis can also complicate transfusion, especially in patients who are IgA-deficient. Finally, iron overload, alloimmunization, and acute and delayed hemolytic transfusion reactions can occur in the setting of ABO and other antigen incompatibility and increase with repeated RBC transfusions (33). Adherence to proper blood transfusion guidelines is essential to conserve blood products and decrease shortages (81).

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Under what circumstances should patients be hospitalized for management of IDA?

Although ID is primarily managed in the outpatient setting, expedited administration of IV iron or even RBC transfusion may be required in patients with acute and significant bleeding. Patients presenting with IDA who require hospitalization include those with signs and symptoms of inadequate oxygen delivery (hemodynamic instability, syncope, chest pain, altered mental status), those with cardiovascular comorbidities (history of HF or MI), or those with an abrupt decrease in Hgb level to less than 7 to 8 g/dL, which suggests rapid blood loss (81). Urgent GI assessment may be warranted to identify and achieve hemostasis through cauterization, ablation, and surgical clips if indicated. Gynecology consultation is indicated in those with persistent HMB and may require use of high-dose hormonal agents, uterine curettage, tamponade, or uterine artery embolization, among other interventions (86).

How should patients with IDA be monitored?

Ferritin level should be assessed around 4 to 6 weeks after infusion and monitored at least every 3 months for the first year after administration of IV iron, or more frequently in those with ongoing bleeding (87). The underlying cause of ID should be identified to prevent recurrence.

When should a specialist be consulted for management of IDA?

Early referral to a hematologist should be considered for high-risk patients (those with IBD, bariatric surgery, CKD, or HFrEF; pregnant patients; and patients in the perioperative period) and/or if the primary clinician is uncomfortable with prescribing or unable to prescribe IV iron. In addition, patients in whom the underlying cause of ID cannot be identified, especially those requiring multiple recurrent infusions or those who do not respond to IV iron, should also be referred to a hematologist for consideration of alternate obscure inherited and acquired disorders and to evaluate for concurrent causes of anemia.

Treatment... Oral iron is recommended as first-line treatment for uncomplicated ID, although tolerance may be limited by GI toxicity. Response to and tolerance of oral iron should be assessed at 4 to 12 weeks using serum ferritin and Hgb parameters. IV iron is recommended in patients who are refractory to and/or intolerant of oral iron and should be considered as first-line treatment in patients with malabsorptive conditions, in those requiring rapid correction (pregnant patients, patients in the preoperative period, and those with chronic or significant bleeding), and in chronic inflammatory conditions such as CKD and HFrEF. In addition to correcting the underlying cause of ID, patients should be monitored for treatment response and to prevent recurrence.

CLINICAL BOTTOM LINE

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What do professional organizations recommend?

Due to limited evidence, guidelines on screening, diagnosis, and treatment vary. Guidelines from CDC, FIGO, and EHA suggest screening for asymptomatic ID in high-risk persons, including adolescents and adults of menstruating potential, pregnant women, and patients in the preoperative period (22, 26, 27). In contrast, the USPSTF recommends against routine screening (25). As discussed earlier, the optimal ferritin thresholds for diagnosis and treatment also vary across recommendations from WHO, AGA, and EHA (24, 43, 49). Disease-specific diagnostic thresholds are available from KDIGO for CKD and from ACC/AHA for HFrEF (53, 54). Recent consensus reviews from AGA and other experts in the field have attempted to define optimal management of ID, including indications for oral and IV supplementation (55, 61, 87).

In the Clinic
Tool Kit

Iron Deficiency Anemia

Patient Information

https://www.nhlbi.nih.gov/health/anemia
https://www.nhlbi.nih.gov/es/salud/anemia
Patient information on anemia and iron deficiency anemia in English and Spanish from the National Heart, Lung, and Blood Institute.

https://www.hematology.org/education/patients/anemia/iron-deficiency
Resources for patients on anemia and iron deficiency anemia from the American Society of Hematology.

Information for Health Professionals

https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/iron-deficiency-anemia-in-pregnant-women-screening-and-supplementation
U.S. Preventive Services Task Force recommendation statement on screening and supplementation for iron deficiency and iron deficiency anemia during pregnancy.

https://www.cdc.gov/mmwr/preview/mmwrhtml/00051880.htm
Recommendations to prevent and control iron deficiency in the United States from the Centers for Disease Control and Prevention.

https://onlinelibrary.wiley.com/doi/10.1002/hem3.108
Recommendations for diagnosis, treatment, and prevention of iron deficiency and iron deficiency anemia from the European Hematology Association.

https://www.who.int/news-room/fact-sheets/detail/anaemia
World Health Organization fact sheet on anemia for health professionals.

WHAT YOU SHOULD KNOW ABOUT IRON DEFICIENCY ANEMIA

What Is Iron Deficiency Anemia?

Red blood cells carry hemoglobin, an iron-rich protein that attaches to oxygen in the lungs and carries oxygen to tissues throughout the body. Anemia occurs when you do not have enough red blood cells or when your red blood cells do not function properly. Iron deficiency anemia (IDA) is a common type of anemia caused by low or improperly functioning iron levels, most commonly due to blood loss.

What Are the Risk Factors?

You may be at higher risk for IDA if you are at risk for blood loss or have poor intake or absorption of iron-rich foods. Those at risk include:

- Females who menstruate, particularly if menstrual periods are heavy
- People who are pregnant or breastfeeding or those who have recently given birth
- People with recent major surgery or physical trauma, including repetitive foot strike in athletes
- People with gastrointestinal (GI) diseases, such as celiac disease; inflammatory bowel diseases, such as ulcerative colitis or Crohn disease; peptic ulcer disease; colon polyps; or other GI abnormalities that can lead to bleeding
- People with a history of bariatric procedures, especially gastric bypass operations
- Vegetarians, vegans, and other people whose diets do not include iron-rich foods (meat, poultry, and fish)
- People with low access to or intake of iron-rich foods due to social or economic reasons

What Are the Symptoms?

Common symptoms include feeling tired or weak; having low mental and work performance, such as difficulty concentrating or thinking clearly; or having unusual cravings for ice, soil, or paper products. More severe symptoms include feeling dizzy or lightheaded, having difficulty breathing, or a racing heart rate. Physical changes might include looking pale; changes in your skin, mouth, or tongue; or hair loss.

How Is It Diagnosed?

IDA is usually diagnosed through blood testing. Your doctor will ask you about your medical history and give you a physical examination. You will get blood tests, and depending on the results of the initial blood tests, you may have follow-up testing, which may include tests of your GI tract, to understand what caused the IDA.

How Is It Treated?

IDA is treated by increasing iron supplementation either by mouth or intravenously. Blood transfusions may be needed in extreme cases.

Questions for My Doctor

- What symptoms should I watch out for that may point to something more serious?
- Do I need to have other tests?
- How often should I get a follow-up check-up?
- Should I follow up with a specialist?

For More Information

ACP
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National Heart, Lung, and Blood Institute
https://www.nhlbi.nih.gov/health/anemia
https://www.nhlbi.nih.gov/es/salud/anemia

American Society of Hematology
https://www.hematology.org/education/patients/anemia/iron-deficiency

Patient Information