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## INTRODUCTION

More than a quarter of the world's population is anemic, with about one-half of the burden from iron deficiency. The prevention and treatment of iron deficiency is a major public health goal, especially in women, children, and individuals in low-income countries.

Challenges in the treatment of iron deficiency include finding and addressing the underlying cause and the selection of an iron replacement product that meets the needs of the patient.

This topic review discusses the management of iron deficiency anemia in adults. The causes and diagnosis of iron deficiency in adults are presented separately. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults".)

Separate topic reviews also discuss treatment of iron deficiency in specific populations:

- **Infants and young children** – (See "Iron deficiency in infants and children <12 years: Treatment".)
- **Adolescents** – (See "Iron requirements and iron deficiency in adolescents".)
- **Pregnancy** – (See "Anemia in pregnancy".)
- **Chronic kidney disease** – (See "Treatment of iron deficiency in hemodialysis patients".)
- **Inflammatory bowel disease** – (See "Vitamin and mineral deficiencies in inflammatory bowel disease", section on 'Iron'.)
- **Bariatric surgery** – (See "Bariatric surgery: Postoperative nutritional management".)
- **Malignancy** – (See "Role of erythropoiesis-stimulating agents in the treatment of anemia in patients with cancer", section on 'Iron monitoring and supplementation'.)

Prevention of iron deficiency in certain at-risk populations is also presented in separate reviews. (See "Introducing solid foods and vitamin and mineral supplementation during infancy" and "Persistent diarrhea in children in resource-limited countries".)

## INITIAL CONSIDERATIONS

**Indications for treatment** — Regardless of the presence of symptoms, all patients with iron deficiency anemia and most with iron deficiency without anemia should be treated [1]. The rationale is that there is risk for further organ damage/ischemia and progression of anemia unless the underlying cause of the deficiency is addressed and adequate iron stores are replenished. An exception is when iron depletion is used therapeutically (eg,

porphyria cutanea tarda, polycythemia vera). (See "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Management and prognosis", section on 'Phlebotomy' and 'Myeloproliferative neoplasms' below.)

**Anemia** — Some patients with iron deficiency anemia will be asymptomatic; others will have symptoms that may include the following:

- Symptoms of anemia, which may include weakness, headache, decreased exercise tolerance, fatigue, irritability, or depression
- Neurodevelopmental delay (children)
- Pica and pagophagia (ice craving)
- Beeturia (reddish urine after eating beets)
- Restless legs syndrome

Similar symptoms, especially fatigue and exercise intolerance, can also be present in individuals who are iron deficient but not anemic. These symptoms and their pathophysiology are discussed in detail separately. (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis", section on 'Clinical manifestations of IDA' and "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Clinical manifestations'.)

When treatment is indicated, the usual approach is repletion of iron. Blood transfusion should **not** be used a treatment for iron deficiency unless the individual has severe anemia with hemodynamic instability. (See 'Severe/life-threatening anemia' below.)

**Iron deficiency without anemia** — Some individuals with reduced or absent iron stores who have not yet developed anemia may have symptoms such as fatigue or reduced exercise tolerance.

The approach to therapy is individualized according to etiology and severity of iron deficiency. We replace iron stores in most patients who have iron deficiency without anemia, with the rationale that this treatment is likely to improve symptoms, and failure to treat is likely eventually to result in anemia. These patients are often referred to the hematologist after iron studies reveal iron deficiency as part of screening laboratory tests performed to evaluate fatigue or unexplained microcytosis.

The benefit of iron replacement for iron deficiency-associated fatigue without anemia has been demonstrated in several small trials and observational studies:

- A trial randomly assigned 90 non-anemic premenopausal women with fatigue, serum ferritin ≤50 ng/mL, and hemoglobin ≥12.0 g/dL to receive a cumulative dose of 800 mg of intravenous (IV) iron or placebo over two weeks [2]. Six weeks after treatment initiation, fatigue was improved in the IV iron arm (decrease of 1.1 versus 0.7 on a 10-point scale, from a baseline of 4.5 in both groups). The effect was more pronounced in those with a baseline serum ferritin ≤15 ng/mL. Benefits of iron supplementation persisted at 12 weeks. Adverse events were greater in the IV iron group (21 versus 9 percent), but none were considered serious. As expected, the IV iron group had increased ferritin (mean increase, 98 ng/mL) and the placebo group did not. Observational studies have also reported improvement in symptoms in non-anemic premenopausal women with low ferritin who were treated with IV iron [3].

- Three trials, which randomly assigned groups of nonanemic women with low ferritin to oral iron supplementation (typically 80 mg of elemental iron daily) versus placebo or a high-iron diet, all reported

improvement in fatigue with oral iron [4-6]. The trial that used dietary iron as a comparator also found improvement with dietary iron, but mean increases in ferritin were greater in the supplement group [4].

- Additional trials in runners and blood donors have demonstrated that iron repletion can improve athletic performance, sleep disturbance, and fingernail breakage [7-9]. (See 'Athletes' below.)

These data are supportive of the above recommendation that iron should be repleted in those with iron deficiency without anemia. The importance of finding the source of blood loss or iron loss also applies in these individuals. (See 'Source of deficiency/blood loss' below.)

Routine iron administration to individuals without iron deficiency is not advised. Rarely, some experts will treat a patient who has symptoms compatible with iron deficiency (pagophagia [ice craving] or restless legs syndrome) without overt laboratory evidence of reduced iron stores if all other interventions have been exhausted. (See "Treatment of restless legs syndrome and periodic limb movement disorder in adults", section on 'Iron replacement'.)

**Source of deficiency/blood loss** — Treatment of iron deficiency and iron deficiency anemia involves more than simply replacing iron. In **all patients**, the cause of iron deficiency must be identified and addressed. This is especially true for men and non-menstruating women, in whom new onset iron deficiency is strongly suggestive of blood loss from an occult gastrointestinal malignancy or other bleeding lesion.

- **Dietary deficiency** – Infants and young children may not receive adequate dietary iron if they are exclusively given cow's milk, breast milk, or formula that is not supplemented with iron. For adults in resource-rich countries, dietary iron deficiency is exceedingly rare because of iron availability in many meats (as heme iron) and vegetables (as non-heme iron), along with routine supplementation of grains with iron. (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis".)

- **Impaired absorption** – Certain gastrointestinal conditions may lead to iron deficiency due to impaired absorption. Examples include inflammatory bowel disease, gastric bypass surgery, celiac disease, and autoimmune gastritis. (See "Vitamin and mineral deficiencies in inflammatory bowel disease" and "Diagnosis of celiac disease in adults" and "Gastritis: Etiology and diagnosis" and "Bariatric surgery: Postoperative nutritional management".)

- **Pregnancy** – Pregnancy results in increased iron requirements for fetal/placental development and to increase maternal red blood cell mass. Total iron loss associated with pregnancy and lactation is approximately 1000 mg. Iron deficiency is common in pregnancy, especially in women with multiple pregnancies and/or borderline iron status prior to pregnancy. (See "Anemia in pregnancy".)

- **Bleeding** – Bleeding is the most common cause of iron deficiency in adults. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults".)

    - **Menstruating women** – Normal menstruation does not lead to iron deficiency unless associated with an iron-restricted diet, such as in a vegan who does not take an iron supplement. However, abnormal uterine bleeding/menorrhagia has been reported to cause iron deficiency anemia in one-fifth to two-thirds of affected women. Approaches to determining the site and cause of bleeding are presented separately. (See "Abnormal uterine bleeding: Management in premenopausal patients" and "Abnormal uterine bleeding in adolescents: Evaluation and approach to diagnosis", section on 'Approach to diagnosis'.)

- **Other known bleeding site** – Other known bleeding sites include gastrointestinal lesions, telangiectasias associated with hereditary hemorrhagic telangiectasia (HHT, also called Osler-Weber-Rendu syndrome), and renal pulmonary syndromes. Specific lesions may be amenable to surgical or medical intervention in some cases. (See "Causes of upper gastrointestinal bleeding in adults" and "Clinical manifestations and diagnosis of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)" and "The diffuse alveolar hemorrhage syndromes".)

- **Adults without an obvious source of blood loss** – Adults without an obvious source of blood loss must be evaluated for occult gastrointestinal malignancy unless there is a clear reason not to do so. This is especially true for individuals >50 years of age, nonmenstruating women, and those at increased risk of colorectal or other gastrointestinal cancers based on family history or other risk factors. The approach to endoscopy will vary with patient characteristics and practice patterns by the gastroenterology consultant. Many perform upper and lower endoscopy on all patients, with capsule endoscopy if those procedures are uninformative. An evaluation is not complete until a site of blood loss is found or until negative upper and lower endoscopy and capsule endoscopy results are found. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors", section on 'Risk factors' and "Evaluation of occult gastrointestinal bleeding".)

The likelihood of a gastrointestinal source of bleeding such as colorectal cancer depends on the individual's age, other risk factors, and when (if ever) their most recent screening was performed. In a series of 142 adults referred to a single hospital system for iron deficiency anemia, nine (6.3 percent) had colorectal cancer [10]. Other diagnoses included gastritis (46 percent), duodenitis, including *Helicobacter pylori* (24 percent), and benign colon lesions such as hemorrhoids. There was one diagnosis of esophageal cancer. Only seven did not have a source identified. Those with a diagnosis of autoimmune gastritis have an increased incidence of gastric cancer requiring regular screening.

**Role of diet** — Individuals may ask about the role of diet in preventing or treating iron deficiency.

- **Prevention** – A normal healthy diet has sufficient iron to meet normal requirements. While strict vegetarian diets contain less iron than those containing meat, the fortification of flour with iron usually mitigates iron deficiency, unless there are losses through bleeding. An iron containing multivitamin is usually adequate to maintain iron losses through normal menstruation.

- **Treatment** – The iron content of foods is unlikely to be sufficient to replete iron stores in an individual with iron deficiency. Even foods high in iron, such as fortified cereals and organ meats, contain only a few milligrams of iron ( table 1). In contrast, oral and intravenous iron formulations will provide full replacement when administered as described below. (See 'Iron replacement products' below.)

Additional information that may help educate patients about iron deficiency is presented separately. (See "Patient education: Anemia caused by low iron in adults (Beyond the Basics)", section on 'Iron and diet'.)

## PATIENT POPULATIONS

**Severe/life-threatening anemia** — Patients with severe, severely symptomatic, or life-threatening anemia should be treated with red blood cell (RBC) transfusion because correction of iron deficiency anemia using iron replacement requires time for iron administration and incorporation into RBCs. (See "Indications and hemoglobin thresholds for red blood cell transfusion in the adult".)

RBC transfusion can be life saving for the patient who is hemodynamically unstable due to active bleeding, and/or when evidence of end-organ ischemia secondary to severe anemia is present ( algorithm 1). The following may be expected for each unit of packed RBCs transfused to an adult, as long as there is not ongoing bleeding:

- Total volume – 300 mL
- Volume of RBCs – approximately 200 mL
- Iron – 200 mg (in the form of hemoglobin)
- Increase in hemoglobin – approximately 1 g/dL
- Increase in hematocrit – approximately 3 percentage points

Once the patient is stabilized with transfusion, the need for additional iron supplementation can be determined and evaluation for the cause can be pursued.

**Infants/young children** — (See "Iron deficiency in infants and children <12 years: Treatment".)

**Adolescents** — (See "Iron requirements and iron deficiency in adolescents", section on 'Management'.)

**Pregnancy** — Iron requirements increase during pregnancy, in order to accommodate fetal and placental needs, expansion of the maternal RBC mass, and blood loss during delivery [11]. Treatment of iron deficiency in pregnant women is important for both the mother and the developing fetus, and iron repletion should occur promptly. Our approach to the evaluation and treatment of iron deficiency in pregnant and postpartum women is presented in detail separately. (See "Anemia in pregnancy".)

**Older adults** — Older individuals may become iron deficient for a number of reasons. As noted above, a search for the cause of new onset iron deficiency is mandatory for all older individuals for whom a new underlying lesion would be treated. (See 'Source of deficiency/blood loss' above.)

Older individuals may also have a higher incidence of intolerance to oral iron supplementation, especially with constipation, as well as reduced absorption of oral iron, especially if they are taking antacids or have impaired gastric acid production.

There is a lack of high-quality evidence guiding dosing and administration in older adults. Our approach is as follows [12]:

- We have a low threshold for administering iron intravenously in older adults. In circumstances where intravenous iron may not be an immediate option (patient preference for a trial of oral therapy, third-party payor issues) oral iron may be used with the recognition that intravenous iron may ultimately be required if oral iron is poorly tolerated or ineffective. (See 'Uses for IV iron' below.)

- Oral iron should be administered no more frequently than once daily, and every-other-day therapy may be equivalent and likely more effective than once-daily dosing. (See 'Dosing and administration (oral iron)' below.) Further, alternate day therapy is associated with fewer gastrointestinal side effects.

- Lower doses of oral iron may be effective and at the same time cause less gastrointestinal toxicity. In a randomized trial in 90 hospitalized patients >80 years of age who had iron deficiency anemia, daily doses of 15, 50, or 150 mg of elemental iron for two months were equally effective in raising hemoglobin and ferritin concentrations, while adverse side effects were significantly less common at the lower iron doses [13]. As noted below, we use dosing on alternate days rather than daily. As an example, a dose of oral iron elixir may

be given on Monday, Wednesday, and Friday. (See 'Dosing and administration (oral iron)' below and 'Strategies to improve tolerability' below.)

**Inflammatory bowel disease** — Iron deficiency and iron deficiency anemia may affect a significant proportion of individuals with inflammatory bowel disease (IBD), especially those with ulcerative colitis. (See "Vitamin and mineral deficiencies in inflammatory bowel disease".)

We favor IV iron for individuals with IBD, especially those with significant disease activity or more severe anemia, for the following reasons [14,15]:

- Many individuals with IBD have severe intolerance to oral iron preparations, which may also worsen IBD disease activity. In a retrospective review of 277 individuals with IBD who were treated with oral iron, intolerance to therapy was seen in one-fourth [16]. In a series of 19 individuals with IBD who were randomly assigned to receive IV iron sucrose or oral ferrous fumarate, the oral iron was associated with increased disease activity, worse wellbeing score, and increased abdominal pain [17].

- Individuals with IBD may have ongoing inflammation and/or malabsorption that may interfere with iron absorption, and IV iron is better able than oral iron to partially overcome the iron-restricted erythropoiesis associated with inflammation.

- Use of IV rather than oral iron may be associated with better preservation of a healthy gut microbiome [18].

Numerous studies in the United States and other countries have demonstrated the safety and efficacy of various IV iron formulations [19-22]. This practice is consistent with recommendations from several expert panels [23-26]. In Europe, IV iron is standard frontline therapy for IBD-associated iron deficiency [15]. Of the IV iron formulations, iron sucrose has been extensively studied in IBD, although ferric carboxymaltose, LMW iron dextran, iron isomaltoside and ferumoxytol have all been shown to be effective and can be administered in a brief, single visit [17,22,27-29]. A single dose administration increases convenience, obviates the need for multiple intravenous line placements, and potentially decreases costs of care.

Oral iron may be used in individuals for whom IBD disease activity and anemia are mild, those who wish to avoid the costs and inconvenience associated with IV iron, those who wish to determine their tolerance of oral iron before using IV iron, and those for whom intolerance of oral iron is not a concern. If oral iron is used in IBD, ferric maltol may be better tolerated [30].

**Following gastrointestinal/bariatric surgery** — Gastric bypass and other gastric surgeries, such as partial resection for ulcer disease or gastrectomy for gastric cancer, increase the risk of iron deficiency, as well as numerous other vitamin and mineral deficiencies. (See "Vitamin and mineral deficiencies in inflammatory bowel disease", section on 'Iron'.)

The mechanism is mainly due to the removal or bypass of intestinal tissues needed for nutrient absorption, particularly the duodenum, the richest source of ferroportin. For patients who have undergone gastric resection, reduced gastric acid production further contributes. In the stomach, iron is normally conjugated to compounds (amino acids, sugars, vitamin C) that protect it from conversion to ferric hydroxide (rust) by the alkaline secretions from the pancreas, which are necessary for normal digestion [31]. Gastrectomy may also be associated with perioperative blood loss.

We prefer IV rather than oral iron for most patients who have undergone gastric resection, Roux-en-Y, biliopancreatic diversion, or similar procedures, as it ensures adequate delivery and avoids gastrointestinal

toxicities, which may be especially burdensome in these patients. Some patients, especially those having undergone minimally invasive procedures such as gastric banding, may tolerate oral iron. However, multiple gastrointestinal perturbations are often present, and IV iron may simplify care. For those for whom IV iron is not available, additional strategies for improving absorption and tolerability may be required. (See 'Strategies to improve tolerability' below.)

We also prefer IV rather than oral iron for most patients who have anemia following gastrectomy for similar reasons. The efficacy of IV iron was demonstrated in a trial that randomly assigned 454 patients who underwent gastrectomy for gastric cancer and had anemia (hemoglobin from 7 to 10 g/dL) within the week after the surgery to receive IV iron (ferric carboxymaltose, 1000 mg if body weight was ≥50 kg; 500 mg if body weight was <50 kg) or placebo [32]. Compared with the placebo group, the IV iron group was less likely to require additional treatment for anemia (oral iron in 4.1 versus 0 percent; transfusions in 1.8 versus 1.4 percent). There were no serious adverse events (mild to moderate urticaria and injection site reactions in 10 percent), and quality of life was similar between the two groups.

**Perioperative** — Perioperative patients may have anemia from blood loss, and others may have undiagnosed iron deficiency that becomes apparent during the perioperative evaluation.

Perioperative iron administration has been demonstrated to reduce the degree of anemia and in some cases to reduce transfusions in a variety of other types of surgery. The reduction in transfusions appears to be greatest in those with preoperative anemia, and we would administer IV iron to individuals with preoperative anemia if the estimated surgical blood loss is likely to be significant and iron deficiency is demonstrated to be the cause (or likely cause).

Randomized trials include the following:

- In a trial that randomly assigned 487 individuals with anemia prior to elective open abdominal surgery to receive one dose of IV ferric carboxymaltose or placebo ≥10 days before surgery, the hemoglobin was higher in the IV iron group (approximately 0.5 g/dL higher by the time of surgery and approximately 1.1 g/dL higher at 8 weeks) [33]. Although the manuscript did not define the transfusion protocol, and the transfusion rate was 30 percent, (twice the expected rate for abdominal surgery) there were no differences in the frequency of transfusion and/or death, or in the length of hospital stay, complication rate, or quality of life. Approximately one-fifth of participants were taking oral iron already, suggesting that iron deficiency may have been at least partially corrected, and at least one-fourth of participants did not have iron deficiency based on preoperative iron studies. The study was not powered to determine whether iron-deficient patients have a lower transfusion rate after preoperative IV iron; however, the results suggest that administration of IV iron to all anemic individuals does not necessarily reduce transfusion rates.

  A Cochrane review that preceded this trial also found an increase in hemoglobin and no difference in transfusions, with IV iron, but numbers were very small (372 participants in total) [34].

- In a trial that randomly assigned 201 patients undergoing elective surgery who had anemia and evidence of iron deficiency (ferritin <100 ng/mL or transferrin saturation <20 percent) to receive or not receive IV ferric carboxymaltose along with standard care, the hemoglobin level four weeks postoperatively was greater in the IV iron group (12 versus 13 g/dL) [35]. The proportion who were transfused was also lower in the IV iron group (5 versus 1 percent), although this may have been affected by knowledge of the assignment to IV iron.

Other trials in specific surgical populations have also been conducted, as discussed separately. (See "Perioperative blood management: Strategies to minimize transfusions", section on 'Iron deficiency anemia'.)

As with other individuals, determining the cause of anemia and, for those with iron deficiency, the underlying cause of the deficiency, is an essential component of management. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Search for source of blood and iron loss' and "Diagnostic approach to anemia in adults".)

**H. pylori, peptic ulcer disease, and gastritis** — *H. pylori* infection, autoimmune gastritis, and celiac disease are chronic conditions of which the patient may be unaware. These conditions are common causes of iron deficiency in individuals without a source of blood loss, and they can interfere with oral iron absorption [36]. Individuals who have a blunted or incomplete response to oral iron therapy may be tested for these conditions, as discussed below. (See 'Approaches to lack of response' below.)

Details of the evaluation and treatment for these conditions are presented separately:

- ***H. pylori*** – (See "Indications and diagnostic tests for Helicobacter pylori infection in adults" and "Treatment regimens for Helicobacter pylori in adults".)
- **Autoimmune gastritis** – (See "Metaplastic (chronic) atrophic gastritis".)
- **Celiac disease** – (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults" and "Diagnosis of celiac disease in adults" and "Management of celiac disease in adults".)

We do not delay iron replacement while treating *H. pylori* infection and/or awaiting resolution of an ulcer or gastritis (iron repletion can commence simultaneously with treatment). Intravenous iron may be more effective and may simplify care, especially if oral iron absorption is impaired or if gastrointestinal side effects interfere with adherence to therapy. (See 'Oral versus IV iron' below.)

**Chronic kidney disease** — IV iron is the current standard in both dialysis- and nondialysis-associated chronic kidney disease (CKD). The rationale includes a number of biological and practical aspects of CKD, including impaired oral absorption, frequent use of calcium-containing salts and antacids, ongoing blood loss, synergism with erythropoiesis-stimulating agents (ESAs), and frequent visits and established IV access in individuals undergoing hemodialysis. This subject, and dosing for patients with CKD, is discussed in detail separately. (See "Treatment of iron deficiency in nondialysis chronic kidney disease (CKD) patients", section on 'Treatment' and "Treatment of iron deficiency in hemodialysis patients", section on 'Dosing and administration'.)

**Cancer** — There are numerous causes of anemia in patients with cancer, including chronic inflammation, impaired absorption of nutrients, hemolysis, and iron deficiency, often caused by bleeding. (See "Causes of anemia in patients with cancer".)

Effective therapies for cancer-associated anemia include treatment of the malignancy, blood transfusion, and erythropoiesis-stimulating agents (ESAs). For individuals with cancer who have iron deficiency and are receiving an ESA, we generally use IV iron due to its greater synergy with ESAs compared with oral iron [37,38]. This practice is supported by a 2012 National Comprehensive Cancer Network (NCCN) practice guideline for cancer- and chemotherapy-induced anemia, which notes that IV iron appears to have superior efficacy compared with oral iron [39]. This subject is discussed in more detail separately. (See "Role of erythropoiesis-stimulating agents in the treatment of anemia in patients with cancer", section on 'Iron monitoring and supplementation'.)

There is limited evidence to guide practice for iron supplementation in patients with cancer who are not receiving an ESA [38,40,41]. Treatment is individualized. An observational study in anemic cancer patients receiving IV iron (ferric carboxymaltose, median dose 1000 mg of elemental iron) indicated that patients with baseline hemoglobin levels up to 11.0 g/dL and serum ferritin levels up to 500 ng/mL had an increase in hemoglobin and a reduction in the need for blood transfusions [42]. Benefit was also noted for those with ferritin levels >500 ng/mL if transferrin saturation was <20 percent (mean baseline saturation, 14 percent). IV iron was well tolerated, with adverse drug reactions, mainly nausea and diarrhea, reported in 2.3 percent.

**Myeloproliferative neoplasms** — Iron deficiency is not a problem during early stages of myeloproliferative syndromes, and iron should not be repleted in individuals undergoing therapeutic phlebotomy as a means of controlling polycythemia. An exception may be an individual with symptoms related to iron deficiency such as severe restless legs syndrome, pagophagia or pica, which may be treated with judicious use of oral (or sometimes IV) iron.

In contrast to the polycythemia, which characterizes early stages of myeloproliferative neoplasms (MPNs), individuals can develop iron deficiency anemia later in the course of an MPN. This is especially common in individuals with longstanding polycythemia vera (PV), who are likely to have been treated with multiple phlebotomies, as well as individuals with primary myelofibrosis. In these circumstances, the replacement of iron is prudent. In addition to iron deficiency, individuals with MPNs may also have a source of bleeding, which should be investigated, and/or concomitant deficiencies of vitamin B12 or folate, which should be addressed [43]. As noted below, transferrin saturation is a more reliable indicator of iron need than serum ferritin. (See 'Monitoring and hemoglobin/iron targets' below.)

**Heart failure** — Anemia is a frequent finding in patients with heart failure (HF) and can worsen cardiac function and exacerbate symptoms. An approach to management of anemia (including iron deficiency anemia) in the setting of HF, evidence for the benefits and risks of IV iron supplementation, and society guidelines for this population are discussed in depth separately. (See "Evaluation and management of anemia and iron deficiency in adults with heart failure", section on 'Treatment'.)

**Athletes** — Athletes can develop iron deficiency and anemia by a number of mechanisms including occult blood loss, hemolysis, and production of inflammatory cytokines. (See "Overtraining syndrome in athletes", section on 'Anemia and iron deficiency' and "Diagnostic approach to anemia in adults", section on 'Ways to approach the diagnosis'.)

Therapy includes nutritional counseling and iron repletion [44,45]. A meta-analysis that evaluated iron replacement in endurance athletes with iron deficiency without anemia found therapy to be effective in improving laboratory markers of iron status and oxygen utilization [9]. (See 'Iron deficiency without anemia' above.)

## IRON REPLACEMENT PRODUCTS

**Oral versus IV iron** — The choice between oral and intravenous (IV) iron depends on a number of factors including the acuity of the anemia, costs and availability of different iron replacement products, as well as the ability of the patient to tolerate oral iron preparations ( table 2). Most patients are treated with oral iron because it is generally effective, readily available, inexpensive, and safe. However, up to 70 percent of patients for whom oral iron is prescribed (especially ferrous sulfate) report gastrointestinal side effects [46]. (See 'Side effects (oral iron)' below.)

We generally treat patients with uncomplicated iron deficiency anemia with oral iron due to the ease of administration, as illustrated in the treatment algorithm ( algorithm 1). However, practice in some populations is evolving [31]. There are several settings in which oral iron may be ineffective and/or poorly tolerated, and the safety of IV iron formulations is much improved over that seen historically with products such as high molecular weight iron dextran (HMW ID), which was associated with anaphylaxis and shock, including fatal events, and which has been removed from the market. The availability of IV iron formulations with improved toxicity profiles has lowered the threshold at which many patients would consider switching from an oral to an IV preparation.

Settings in which one route or the other may be preferable include the following:

- **Oral**
  - Oral supplements are the only form of iron available to many patients, especially those in under-resourced areas.
  - For many patients, oral iron may be more cost effective due to the lack of need for monitored infusion.
  - Use of oral iron avoids the need for IV access and monitored infusion.
  - Use of oral iron eliminates the potential for infusion reactions and/or anaphylaxis.
  - Oral supplements are generally used for infants, children, and adolescents.
- **IV**
  - IV iron is appropriate for patients who are unable to tolerate gastrointestinal side effects of oral iron. Examples include older individuals, individuals with abnormal uterine bleeding in which oral iron cannot keep up with losses, individuals who are pregnant (who may already have gastrointestinal symptoms related to the pregnancy), and individuals with existing gastrointestinal disorders, which may be exacerbated by the gastrointestinal side effects of oral iron. (See 'Side effects (oral iron)' below.)
  - IV iron may be needed for those with severe/ongoing blood loss (eg, telangiectasias, varices).
  - Gastric surgery (bypass, resection) that reduces gastric acid may severely impair intestinal absorption of oral iron.
  - Malabsorption syndromes (celiac disease, Whipple's disease, bacterial overgrowth) may limit absorption of oral iron.
  - In the second trimester of pregnancy, if the Hb is less than 10.5 g, or at any time in the third trimester, at which oral iron is unlikely to supply adequate iron to the developing fetus. (See "Anemia in pregnancy".)

Elevated hepcidin may also reduce oral iron absorption with concomitant inflammatory states [47]. This potential mechanism supports the approach of switching to IV iron in patients with iron deficiency that does not respond to oral iron supplementation. (See 'Uses for IV iron' below and "Anemia of chronic disease/anemia of inflammation", section on 'Iron supplementation'.)

Use of IV iron allows administration of nearly full-replacement doses in one or two infusions, depending on the product ( table 3). In contrast, it has been estimated that the maximum amount of elemental iron that can be absorbed with an oral iron preparation is 25 mg per day [48].

A discussion of oral versus IV iron specific to patients with cancer receiving erythropoiesis-stimulating agents (ESAs) is presented separately. (See "Role of erythropoiesis-stimulating agents in the treatment of anemia in

patients with cancer", section on 'Oral versus parenteral'.)

As noted below, we do not use other routes of administration such as intramuscular or transdermal iron. (See 'Routes we do not use (IM, transdermal)' below.)

**Oral iron**

**Uses for oral iron** — Oral iron provides an inexpensive and effective means of restoring iron balance in a patient with iron deficiency without complicating comorbid conditions. Uses for oral iron supplements include the following:

- Treatment of iron deficiency anemia
- Treatment of iron deficiency without anemia
- Nutritional support to prevent deficiency

In contrast, oral iron may not be effective for individuals with ongoing blood loss, inflammatory bowel disease or gastric bypass, chronic kidney disease, or those with substantial distress from the side effects of oral iron. (See 'Oral versus IV iron' above.)

As noted above, the source of iron deficiency/site of bleeding should be addressed, and a comparison of the advantages and disadvantages of oral versus IV iron are discussed above. (See 'Initial considerations' above.)

**Choice of oral preparation** — Numerous oral iron formulations are available ( table 4), and for the most part all are equally effective, as long as they are taken [31]. The most appropriate form is a liquid (allows for dose titration) or tablet containing ferrous salts. Side effects are generally similar among different preparations. Use of alternate day dosing and a liquid form that can be titrated may reduce side effects. (See 'Dosing and administration (oral iron)' below and 'Side effects (oral iron)' below.)

Examples of available preparations (with the amount of elemental iron per dose) include:

- Ferric maltol – 30 mg tablet contains 30 mg elemental iron
- Ferrous fumarate – 324 or 325 mg tablet (contains 106 mg elemental iron per tablet)
- Ferrous gluconate
  - 240 mg tablet (contains 27 mg elemental iron per tablet)
  - 324 mg tablet (contains 38 mg elemental iron per tablet)
  - 325 mg tablet (contains 36 mg elemental iron per tablet)
- Ferrous sulfate
  - 325 mg tablet (contains 65 mg elemental iron per tablet)
  - 220 mg/5 mL oral elixir (contains 44 mg elemental iron per 5 mL)
  - 75 mg/mL oral solution (contains 15 mg elemental iron per mL)
- Polysaccharide iron complex
  - Various over-the-counter tablets (eg, NovaFerrum 50 contains 50 mg elemental iron per tablet)
  - 15 mg/mL oral solution (contains 15 mg elemental iron per mL)

Additional over-the-counter preparations include heme iron polypeptide, carbonyl iron, ferric citrate, ferrous ascorbate, and ferrous succinate [31]. Among these, there is no evidence that one is more effective than another or has fewer side effects than another. All are relatively inexpensive. Other over-the-counter preparations are also widely available. Preparations such as polysaccharide-iron complex and heme iron are more expensive; these preparations are effective and may have other advantages (such as lack of metallic taste), but in a small randomized trial in young children, ferrous sulfate was slightly more effective than polysaccharide iron complex [49]. (See "Iron deficiency in infants and children <12 years: Treatment", section on 'Oral iron therapy'.)

We do not use enteric-coated or sustained-release capsules, which are poorly absorbed due to iron released too far distally in the intestinal tract; in some cases, the intact tablets are excreted in stool [50]. Iron absorption from the gut mucosal cells occurs via divalent metal transporter 1 (DMT1), a protein localized to the duodenum and upper jejunum. Once in the cell, ferroportin transports the iron across the cell to the blood where it is bound by transferrin. We also do not use preparations such as the heme iron polypeptide ProFerrin, as these have not been evaluated clinically and their cost is greater.

**Dosing and administration (oral iron)** — The paradigm for iron repletion has evolved, as evidence has begun to emerge suggesting that excessive dosing is potentially counterproductive, decreasing iron absorption and increasing side effects without improving iron levels or anemia. (See 'Side effects (oral iron)' below.)

- **Daily versus alternate-day dosing** – We typically advise our patients to take their dose every other day as long as they can manage the schedule appropriately; a reasonable variation on the schedule that is easier to follow is to give the dose on Monday, Wednesday, and Friday.

- **Number of doses per day** – There is no reason to give more than one dose per day.

- **Amount of iron per dose** – The amount of iron in the every-other-day dose or the Monday-Wednesday-Friday dose is also not well established. However, there is not a reason to think higher doses improve absorption, and adverse effects are generally dose related. Thus, we typically use one tablet per dose. The elemental iron content of different formulations is summarized in the table ( table 4). As an example, a 325 mg ferrous sulfate tablet contains 65 mg of elemental iron per tablet, of which approximately 25 mg is absorbed and used in production of heme and other molecules [51].

As noted above, evidence suggests that alternate-day dosing (taking the iron every other day rather than every day) appears to result in equivalent or better iron absorption than daily dosing, usually with fewer adverse effects [51,52].

- Intriguing findings from a 2015 study of the response of 54 iron-deficient women to daily oral iron suggested that giving multiple doses per day could cause a paradoxical decrease in iron absorption [53]. These women with depleted iron stores (ferritin ≤20 ng/mL) but without anemia were given various doses of oral iron that contained a traceable isotope to track absorption. Iron absorption was best when dosing was restricted to lower doses and less frequent administration (40 to 80 mg of iron no more than once a day). Higher or more frequent doses of iron raised circulating hepcidin levels and **reduced** subsequent fractional iron absorption.

- Subsequent randomized trials of women with iron deficiency, with or without anemia, have also documented improved iron absorption with alternate-day dosing compared with every-day dosing [54,55]. As an example, in a 2017 trial in which 40 women were randomly assigned to receive oral iron (60 mg of $FeSO_4$) once daily for 14 days or once every other day for 28 days (same cumulative dose), every-other-day dosing resulted in

**greater** iron absorption (131 versus 175 mg total) [54]. There was a trend towards decreased nausea in the every-other-day group that did not reach statistical significance; constipation was not assessed.

It is possible that individuals assigned to alternate-day dosing are more likely to take the assigned medication; if true, this does not diminish the potential value of this approach [52]. Trials in which participants and investigators are blinded to the dosing interval (eg, using placebo on alternate days) are eagerly awaited.

Some individuals may reasonably choose every-day dosing if they find that it improves tolerability or ease of use.

As noted above, older individuals are more likely to have gastrointestinal toxicity from oral iron, particularly severe constipation, and we often avoid oral iron and administer intravenous iron to older patients when possible. For those who prefer to use oral iron, we are more likely to use lower doses in older individuals. (See 'Older adults' above.)

Many clinicians recommend giving oral iron along with a source of ascorbic acid, either by taking it with orange juice or with a 500 mg ascorbic acid tablet. This is based on the hypothesis that ascorbic acid may increase iron absorption. However, as noted below, some studies show no major impact of lower pH on iron absorption. We do not routinely advise our patients to take vitamin C to increase iron absorption, as we are unaware of high-quality data to support this practice. If oral iron is not being absorbed, we generally switch to intravenous iron and evaluate the patient for other possible reasons for impaired absorption if appropriate. (See 'Approaches to lack of response' below.)

The bioavailability and absorption of oral iron may be enhanced by attention to the following ( table 5) [56-58]:

- **Food** – Phosphates, phytates, and tannates in foods may bind iron and impair its absorption. (See "Regulation of iron balance", section on 'Intestinal iron absorption'.)

    - Iron generally should not be given with food.
    - Iron should especially be taken separately from calcium-containing foods and beverages (milk), calcium supplements, cereals, dietary fiber, tea, coffee, and eggs.

- **pH** – Iron is best absorbed as the ferrous ($Fe^{++}$) salt in a mildly acidic medium. Gastric acidity is helpful, and medications that reduce gastric acid (eg, antacids, histamine receptor blockers, proton pump inhibitors) may impair iron absorption.

    - Iron should be given two hours before, or four hours after, ingestion of antacids.

    In a trial that randomly assigned 440 individuals with iron deficiency anemia to receive iron with or without vitamin C, the increase in hemoglobin level, reticulocytes, or serum ferritin at two weeks was not improved by coadministration of vitamin C [59]. Potential concerns with the trial include lack of blinding, a relatively short window in which to see an effect, and administration of iron three times per day on a daily basis, which may reduce absorption. In a smaller series of 12 individuals treated with iron during intake of a normal or vitamin C-supplemented diet, the absolute dose of vitamin C did not appear to have a major effect on iron absorption, and the increase in iron absorption with vitamin C was modest [60].

As noted above, enteric-coated or sustained-release capsules are less efficient for oral absorption because they release iron too far distally in the intestine (or not at all). As a result, we avoid these formulations. (See 'Choice of oral preparation' above.)

The duration of treatment differs among experts and in different settings. Some stop treatment when the hemoglobin level normalizes because this allows early detection of recurrent anemia from further blood loss (following therapy for a gastric lesion). Others treat for at least six months after the hemoglobin has normalized in order to completely replenish iron stores (following delivery for a multigravid woman). Treatment with oral iron may take as long as six to eight weeks in order to fully ameliorate the anemia, and as long as six months to replete iron stores.

**Side effects (oral iron)** — Gastrointestinal side effects are extremely common with oral iron administration. These include metallic taste, nausea, flatulence, constipation, diarrhea, epigastric distress, and/or vomiting. Patients may also be bothered by itching and by black/green or tarry stools that stain clothing or cause anxiety about bleeding. As a result, compliance with oral iron administration may be low.

The magnitude and impact of these effects were demonstrated in the following:

- A 2015 systematic review and meta-analysis of randomized trials included 6831 patients assigned to receive ferrous sulfate or a comparator (placebo or IV iron) [46]. The odds ratio (OR) of gastrointestinal side effects was higher with ferrous sulfate compared with placebo (OR 2.32; 95% CI 1.74-3.08) or with IV iron (OR 3.05; 95% CI 2.07-4.48). Subgroup analysis of individuals with inflammatory bowel disease or who were pregnant showed similar results. Effects were not well correlated with oral iron dose within the range of doses studied (100 to 400 mg elemental iron).

- A 2013 systematic review included over 10,000 patients receiving different oral iron formulations [61]. Gastrointestinal adverse effects were seen with all oral formulations (ferrous fumarate, 43 percent; ferrous gluconate, 31 percent; ferrous sulfate, 30 percent). Other supplements such as iron protein succinate or ferrous glycine sulfate, which have enteric coating that reduces absorption, had lower frequencies of adverse effects.

- As noted above, a study in older adults found that supplements containing lower amounts of elemental iron were associated with less gastrointestinal toxicity. (See 'Dosing and administration (oral iron)' above.)

Additional concerns with oral iron administration include a possible role for oral iron in altering colonic microflora and/or promoting carcinogenesis; however, no clinically significant association has been demonstrated [46,62].

**Strategies to improve tolerability** — Interventions to reduce the side effects of oral iron and improve tolerability include the following:

- Increasing the interval to every other day if not done already.

- Making dietary modifications (taking iron with food or milk), although this may reduce absorption. (See 'Dosing and administration (oral iron)' above.)

- Switching to a formulation with a lower amount of elemental iron. (See 'Choice of oral preparation' above.)

- Switching from a tablet to a liquid, for which it is easier to titrate the dose. Some clinicians recommend that individuals taking iron elixir swish water in their mouth after the dose to avoid potential staining of tooth enamel.

- Use of a stool softener or bulk-forming laxative ( table 6), timing bowel movements after meals to take advantage of the gastrocolic reflex, and supporting the feet with a stool when having a bowel movement. (See

"Management of chronic constipation in adults" and "Constipation in the older adult".)

Once a tolerated dose is found, the patient can sometimes increase the dose slowly as tolerated.

As noted above, for many populations, another option is switching to IV iron. Use of IV iron eliminates all of the gastrointestinal side effects of iron, which are due to direct effects of iron on the intestinal mucosa. If the patient switches to IV iron, oral iron should be discontinued. (See 'Intravenous iron' below.)

**Intravenous iron**

**Uses for IV iron** — There are a number of settings in which the use of intravenous (IV) iron may be preferable to oral iron [1,63,64]:

- Poor adherence or gastrointestinal side effects of oral iron.
- Prefer to replete iron stores in one or two visits rather than over the course of several months.
- Ongoing blood loss that exceeds the capacity of oral iron to meet needs (heavy uterine bleeding, mucosal telangiectasias).
- Anatomic or physiologic condition that interferes with oral iron absorption.
- Coexisting inflammatory state that interferes with iron homeostasis.

IV iron may be cost effective in many of these settings. However, the vast majority of iron deficient patients worldwide will not have access to IV iron due to lack of infrastructure for its administration. Additionally, some for whom IV iron is appropriate may wish to avoid the potential risks of adverse reactions, including infusion reactions and potential anaphylaxis, shock, and death, although this risk is exceedingly low.

For individuals who do have access to IV iron, administration may reduce the use of blood transfusion, which in turn avoids transfusion-associated risks. This was demonstrated in a 2013 systematic review and meta-analysis of trials that randomly assigned patients to IV iron versus oral iron or no iron [65]. The administration of IV iron arm was associated with a lower frequency of blood transfusions (risk ratio [RR] 0.74; 95% CI 0.62-0.88). The meta-analysis included trials in a number of conditions, including chronic kidney disease, inflammatory bowel disease, cancer, surgery, and pregnancy, among others (see 'Patient populations' above). Additional randomized trials published subsequently, such as a 2016 trial in 252 pregnant women, have also found that compared to oral iron, IV iron has similar efficacy in improving hemoglobin level and fewer adverse events, including markedly reduced gastrointestinal symptoms [66]. (See 'Pregnancy' above.)

Administration of IV iron should only be considered by those adequately conversant with the requirements for test dose, infusion rates, maximum allowed doses, need (if any) for premedication, and familiarity with minor infusion reactions. We avoid IV iron in patients with active infections, as many infectious agents thrive on iron, although evidence addressing this issue is lacking.

**Choice of IV formulation** — A number of intravenous (IV) iron formulations are available, including ferric carboxymaltose (FCM), ferric gluconate (FG), ferumoxytol, iron sucrose (IS), iron isomaltoside (termed ferric derisomaltose in the United States and Australia), and low molecular weight iron dextran (LMW ID) ( table 3).

All of these formulations are equally effective in treating iron deficiency and have a similar safety profile [1,31,67]. Major differences include cost, formulary/purchasing agreements, and number of visits/time required to administer the full dose. We generally prefer LMW ID because of its low cost and ability to administer in a single dose (although the package insert specifies multiple doses; we use a single dose [1]). Others that can be administered as a single dose include FCM, ferumoxytol, and iron isomaltoside. As discussed below, we believe the frequency

of serious adverse events is comparable among products and generally do not consider this feature when choosing among products (see 'Allergic and infusion reactions' below). One exception is high molecular weight iron dextran (HMW ID), which has a greater frequency of allergic reactions [68,69]. HMW ID is no longer available.

- **Cost** – The relative costs of IV iron products may vary depending on local institutional purchasing agreements. In the United States, LMW ID is relatively inexpensive (typically, less than one-third the price of ferumoxytol, one-seventh the price of FCM, and one-tenth the price of ferric derisomaltose). The cost of these agents in Canada and Europe are much lower and largely comparable with each other.

- **Time for administration** – Administration of LMW ID is done over one hour; other products may be infused more rapidly.

- **Number of doses required** – The choice of product may also be influenced by the frequency of office visits. As examples, patients undergoing dialysis or chemotherapy may have frequent office visits during which frequent low doses of FG or IS can be administered. In contrast, patients for whom frequent visits are not otherwise necessary may prefer products that can be administered in one or two visits, such as FCM, ferumoxytol, or LMW ID.

For patients with a history of a reaction to an IV product, many experts would switch to a different IV iron product. We have successfully used different IV products in patients with serious infusion reactions to one product. This is especially true for patients who have received HMW ID, which was associated with more frequent adverse events and is no longer in use.

In our practice, we often use LMW ID because we treat nondialysis patients who often are seen for a single visit. We also use FCM and ferumoxytol, especially if there is insufficient time for a product, which requires a longer infusion time, or if there is a history of a minor infusion reaction to LMW ID.

A comparison among IV iron products in hemodialysis patients is presented separately. (See "Treatment of iron deficiency in hemodialysis patients".)

Examples of trials comparing different IV iron products include the following:

- A 2018 trial randomly assigned 1997 iron-deficient adults to receive ferumoxytol (two infusions of 510 mg for a total of 1020 mg) versus FCM (two infusions of 750 mg for a total of 1500 mg) [70]. Both groups had comparable increases in hemoglobin (approximate increase, 1.5 g/dL). There were no major between-group differences in the rates of moderate-to-severe hypersensitivity reactions, all of which were rare (incidence, <1 percent). There were no episodes of anaphylaxis. There were six deaths, none of which were considered to be treatment related. Compared with ferumoxytol, hypophosphatemia was more common with ferric carboxymaltose (0.4 versus 38.7 percent), but no clinical sequelae related to hypophosphatemia were seen in either group.

- A 2014 trial randomly assigned 605 patients with iron deficiency anemia that did not improve with oral iron therapy to receive ferumoxytol (two doses of 510 mg) or IS (five doses of 200 mg) [71]. The primary endpoint, increase in hemoglobin by ≥2 g/dL any time during five weeks of therapy, was similar between the ferumoxytol and IS groups (84 versus 81 percent). The mean change in hemoglobin was slightly higher with ferumoxytol (2.7 versus 2.4 g/dL). Adverse events were similar between groups.

- Another trial randomly assigned 162 patients with chronic kidney disease and iron deficiency anemia to receive ferumoxytol (two doses of 510 mg) or IS (10 doses of 100 mg if receiving hemodialysis or five doses of

100 mg if not receiving dialysis) [72]. There was no significant difference in the mean change from baseline hemoglobin level (0.8 versus 0.7 g/dL). Adverse events were similar between groups.

Other smaller trials have shown similar findings [73,74].

Additional information regarding dosing and administration of specific products is described in the following sections. (See 'Dosing/administration of specific IV iron preparations' below.)

**Dose calculation (IV iron)** — The dose of iron administered depends on whether the goal is to treat anemia or to fully replace iron stores. Generally, the dose is calculated based on body weight, current hemoglobin level, and amount of elemental iron per milliliter of the iron product. A sample calculation is provided in the figure ( table 7), and product information contains lookup tables based on patient weight and hemoglobin levels.

In practice, there is no evidence that total doses above 1000 mg of elemental iron are clinically useful. This is supported by the results of the FIRM trial, in which a dose of 1020 mg of ferumoxytol (two vials) was compared with 1500 mg of FCM (two vials) [70]. At five weeks, there was a clinically insignificant 0.24 g increment in hemoglobin concentration with the 50 percent higher dose of FCM.

We often give a fixed dose of approximately 1000 mg, which is generally sufficient to treat anemia (typical red blood cell iron deficit between 500 and 1000 mg) and provide additional storage iron without causing iron overload. Whether this dose can be administered as a single (total dose) infusion or requires multiple infusions depends on the specific product.

**Use of premedication** — As noted below, we are concerned that a number of adverse events attributed to IV iron are in fact due to premedications, especially diphenhydramine (see 'Allergic and infusion reactions' below). Diphenhydramine may cause hypotension, somnolence, flushing, dizziness, irritability, nasal congestion, wheezing, and supraventricular tachycardia [75]. As a result, our approach to premedication is as follows:

- We do **not** give any premedications to patients without a history of asthma or more than one drug allergy.
- For patients with asthma or more than one drug allergy, who are at slightly increased risk of an allergic or infusion reaction, we routinely premedicate with 125 mg of methylprednisolone and an H2 blocker (eg, 10 mg of famotidine) given intravenously prior to administration of any IV iron product [76].
- For patients with a history of inflammatory arthritis, we administer methylprednisolone, 125 mg intravenously, and prescribe a short course of prednisone (1 mg/kg per day orally for four days) [76].
- We (and others) do **not** use H1 blockers (antihistamines) to prevent (or treat) infusion reactions [63,77,78].
- We administer every IV iron product slowly at first and observe patients for infusion reactions. Specific infusion durations are described in the sections on individual products.

Treatment of infusion reactions is discussed below. (See 'Allergic and infusion reactions' below.)

**Dosing/administration of specific IV iron preparations**

**LMW iron dextran** — LMW ID (INFeD, CosmoFer) is the least expensive of the IV iron formulations that can be administered in a single, large dose (total dose infusion) ( table 3).

LMW ID can be given as multiple doses of 2 mL (equivalent to 100 mg elemental iron, based on a concentration of 50 mg elemental iron per mL). Whereas this is the approved method, we generally do not use this dosing paradigm due to the multiple visits required and IV line insertions without added benefit of safety or efficacy [79]. LMW ID can also be given as a single, total dose infusion; this practice has been shown to be safe and effective in the settings of heavy uterine bleeding, pregnancy, postpartum, inflammatory bowel disease, gastric bypass, hereditary hemorrhagic telangiectasia, chronic kidney disease, and restless legs syndrome [80-82]. We often give a total dose infusion of 1000 mg in 250 mL of normal saline over one hour. Although this is not a US Food and Drug Administration-approved dosing, we have not observed any serious adverse events with this approach in over 10,000 administrations [80]. We prefer this method of administration over multiple 100 mg doses as it decreases the need for multiple intravenous line placements, possible infusion reactions, and costs.

A test dose is required prior to the first dose of LMW ID (0.5 mL [25 mg]). This may be given gradually over at least 30 seconds; we prefer to administer the test dose over five minutes while observing the patient. If no symptoms occur during the first 5 to 10 minutes, it is extremely unlikely that an infusion reaction will occur. After the test dose, we administer the remainder of a 1000 mg dose over the balance of one hour.

In contrast to LMW ID, we do not use HMW ID, as risks of severe reactions are much greater with the HMW product [83,84]. The HMW product is largely unavailable.

**Ferric gluconate** — Ferric gluconate (FG; Ferrlecit), also called ferric gluconate complex, can be given over multiple infusions. A typical dose is 10 to 15 mL (equivalent to 125 to 187.5 mg elemental iron, based on a concentration of 12.5 mg elemental iron per mL) ( table 3). A test dose is recommended if the patient has a history of drug allergies. While a test dose is not required for patients without a history of drug allergies, we administer all iron formulations slowly at first and observe patients for infusion reactions.

Each dose of 10 to 15 mL can be administered as a two-minute bolus (in patients undergoing hemodialysis) or diluted in normal saline and infused over 20 to 30 minutes. One group has reported administration of 125 mg diluted in 100 mL of normal saline and infused over 30 to 60 minutes [85]. Although rarely done, 250 mg infusions over one hour have been reported to be well tolerated [86]. Larger single doses should not be attempted. This product cannot be given intramuscularly (we do not give any products intramuscularly). For these reasons, while a reasonable option during dialysis in which two to three weekly visits are the norm, we avoid this formulation for outpatients in need of intravenous iron as a way to avoid unnecessary visits.

**Iron sucrose** — Iron sucrose (IS; Venofer) also called iron saccharate, is given over multiple infusions, with a maximum individual dose of 10 to 15 mL (equivalent to 200 to 300 mg elemental iron, based on a concentration of 20 mg elemental iron per mL). A test dose (1.25 mL [25 mg] by slow IV push) is recommended if the patient has a history of drug allergies; otherwise, a test dose is not required.

Doses of 10 mL (200 mg elemental iron) are routinely given over 2 to 15 minutes in dialysis centers; a total of five doses is common [87]. For patients with cancer receiving ESAs, 10 mL may be infused over 60 minutes every two to three weeks. Larger doses (ie, doses above 300 mg) are not recommended [88]. This product cannot be given intramuscularly.

IS has been shown to be safe and effective in settings of dialysis, nondialysis chronic kidney disease, inflammatory bowel disease, chemotherapy-induced anemia, the peripartum period, gastric bypass, heavy uterine bleeding, and a host of other conditions associated with iron deficiency. However, for the same reasons as outlined with ferric gluconate (see 'Ferric gluconate' above), we avoid this formulation for outpatients in need of intravenous iron.

**Ferumoxytol** — Ferumoxytol (Feraheme) is composed of superparamagnetic iron oxide nanoparticles coated with a LMW semisynthetic carbohydrate. It can be given in doses of 17 mL (equivalent to 510 mg of elemental iron, based on a concentration of 30 mg of elemental iron per mL) or as a single dose of 1020 mg ( table 3).

Many patients are treated with two doses of ferumoxytol (510 mg elemental iron per dose) administered three to eight days apart, or a single total dose infusion of 1020 mg given over approximately 30 minutes [89]. This allows the patient to be treated in a single visit rather than two visits, which reduces costs and burdens of administration with similar efficacy and safety. While there is no advantage to the two dose regimen, this is the dosing specified in the product information, and insurance approval may need to be sought prior to administering a total dose infusion of ferumoxytol.

The infusion rate of ferumoxytol was revised from initial product labeling (1 mL per second of the undiluted solution), to a 15-minute infusion requiring dilution in 50 to 250 mL of normal saline or glucose solution. This change was based on postmarketing surveillance reports that documented a large number of infusion reactions with the 17-second infusion [72,90,91]. We initially used an infusion rate of 17 to 30 seconds; this resulted in 3 of 90 patients (3.3 percent) developing hypotension requiring fluid administration. Subsequently, we have given over 1900 doses at an infusion rate of approximately three minutes (90 to 180 seconds) without any adverse events [31]. As noted above, we have treated many patients with a single dose infusion over 30 minutes. In the absence of a clinical trial, it is prudent to follow approved labeling and not to reduce the infusion time below 15 minutes per 510 mg [92-94].

Single dose infusion of ferumoxytol was also shown to be safe in pregnancy. (See "Anemia in pregnancy", section on 'Intravenous iron'.)

Ferumoxytol can cause a brighter signal on magnetic resonance imaging (MRI) scans, which is important to be aware of but does not negatively affect interpretation of the scan. If an MRI is planned within three months of administration, the radiologist should be notified that the patient has received ferumoxytol.

**Ferric carboxymaltose** — Ferric carboxymaltose (FCM; Ferinject, Injectafer) is a colloidal iron hydroxide complex with tighter binding of elemental iron to the carbohydrate polymer than some other IV iron preparations. FCM can be given as a dose of up to 20 mL (equivalent to 1000 mg of elemental iron, based on a concentration of 50 mg of elemental iron per mL) ( table 3); product labeling specifies a maximum dose of 20 mg per kg of body weight.

Doses of FCM may be given over a 15-minute infusion. We often administer a dose of 750 mg (the vial size available in the United States). Approval for the administration of 1000 mg in 15 minutes has been granted, and a new vial size is expected. As with all formulations, we start slowly, observe for signs of allergy or infusion reaction, and if not seen, administer the balance over 15 minutes. If appropriate, a second dose of 750 mg can be given on a different day. The United States package insert recommends a seven-day interval between 750 mg doses. However, this practice is not followed in most European countries, and there is no clinical evidence supporting it. A number of trials have shown efficacy and safety of this agent in iron-deficient patients in a number of different settings including heavy uterine bleeding, postpartum women, nondialysis-dependent chronic renal failure, inflammatory bowel disease, heart failure, chemotherapy-associated anemia without concomitant use of an ESA, and nonresponse to oral iron [42,47,95-101]. Several series have reported use of FCM during pregnancy without serious adverse events [102-104].

Initial experience with FCM raised concerns about hypophosphatemia observed following administration [105]. Subsequently, only rare reports of clinical sequelae related to hypophosphatemia have been reported, and the clinical significance of hypophosphatemia remains to be defined [106-112]. Serum phosphate levels may need to be monitored in selected populations such as those with borderline phosphate levels at baseline or those receiving repeated doses of FCM [113]. The mechanism of hypophosphatemia appears to involve increased urinary phosphate excretion caused by an increase in serum levels of fibroblast growth factor 23 (FGF-23) and subsequent reduced levels of circulating 1,25-dihydroxyvitamin D [110].

**Iron isomaltoside/ferric derisomaltose** — Iron isomaltoside, which has been renamed ferric derisomaltose (Monofer, Monoferric), has a matrix structure that results in tight iron binding and slow release of labile free iron, allowing administration in a single infusion, at a dose of 20 mg/kg, over 15 minutes. A test dose is not required. The elemental iron concentration is 100 mg/mL.

Two randomized trials have compared this product with iron sucrose in patients with iron deficiency anemia:

- In the first trial (511 patients), ferric derisomaltose (iron isomaltoside) was given as a single dose infusion of 500 or 1000 mg, depending on body weight and hemoglobin level, and iron sucrose was given as up to five infusions of 200 mg each, depending on body weight and hemoglobin level [114]. A greater number of patients in the iron isomaltoside group had an increase in hemoglobin of ≥2 g/dL (69 versus 52 percent; $p<0.0001$), and serious adverse events did not differ (0.6 percent in both groups).

- In the second trial (1512 patients), all individuals in the ferric derisomaltose (iron isomaltoside) group received a single dose of 1000 mg, and all individuals in the iron sucrose group received approximately five infusions of 200 mg, for a cumulative dose of 1000 mg [115]. The mean increase in hemoglobin at eight weeks was similar in both groups (2.5 g/dL) and fatigue scores improved to a similar degree. Serious adverse events such as hypersensitivity reactions were also similar (0.3 versus 0.4 percent).

In a prospective observational study, ferric derisomaltose (iron isomaltoside) resulted in a more rapid and more pronounced hematologic response compared with iron sucrose [115]. The safety profile was similar, with a low frequency of hypersensitivity reactions and cardiovascular events.

The safety and efficacy have also been reported in selected patient populations:

- Chronic kidney disease [116,117]
- Inflammatory bowel disease [118]
- Cardiac surgery [119]
- Chemotherapy-induced anemia [120]
- Postpartum hemorrhage [121]
- Iron deficiency of mixed etiology [122]

### Allergic and infusion reactions

**Risks/prevention** — IV iron has the potential to cause allergic reactions, including potentially life-threatening anaphylaxis. However, we believe these serious allergic reactions are exceedingly rare and vastly overestimated [1]. We also believe the frequency of serious adverse events is comparable among products, based on published studies and our experience [67,70].

In contrast to serious allergic reactions, IV iron may be associated with non-allergic infusion reactions including self-limiting urticaria, palpitations, dizziness, and neck and back spasm; generally, these occur in <1 percent of

individuals and do not progress to more serious reactions [85]. The non-allergic reaction consisting of flushing of the face and myalgias of the chest and back has been termed the Fishbane reaction [123,124]. The mechanism remains unknown but may be due to activation of complement, referred to as complement activation-related pseudoallergy (CARPA), by the labile free iron, leading to symptoms such as flushing, myalgias of the chest or flank, or sensations of fullness in the throat [125-127].

Similar to allergic reactions, higher rates of non-allergic reactions were seen with high molecular weight (HMW) iron dextran, which is no longer used. Trials involving IV iron product comparisons generally have shown similar rates of these infusion reactions between products. (See 'Choice of IV formulation' above.)

In addition, patients with a history of inflammatory arthritis (eg, rheumatoid arthritis) commonly experience a flare of their arthritis during IV iron infusion, which is usually well-controlled with glucocorticoid premedication and/or a brief course of glucocorticoids (three to four days) following the infusion (see 'Treatment' below). The cause of these exacerbations of inflammatory arthritis is incompletely understood but may involve effects of oxidant stress [128].

Many clinicians are reluctant to use IV iron due to experience in the era before modern products were available, when allergic reactions (including severe reactions) were more common, as well as misunderstanding of the distinction between rate-related infusion reactions and true allergic reactions, which may have been challenging to distinguish when first encountered [77,129]. Further, misinterpretation of a rate-related infusion reaction as an allergic reaction may lead to interventions that convert a minor side effect into a serious adverse event, further reinforcing the mistaken impression that the product is dangerous [75]. In a typical scenario, myalgias, including chest and back discomfort, may be mistakenly ascribed to anaphylaxis, prompting administration of antihistamines and/or epinephrine, which in turn causes tachycardia and/or hypotension, converting the minor reaction to a more serious event.

Further support for the impression that these infusion reactions are not allergic comes from our experience, in which we have measured serum tryptase levels at the time of the reaction, and have found these levels not to be elevated [31,130].

Our approach to reducing the risks of allergic and infusion reactions is as follows [1]:

- We avoid administration of a product to which a patient has had a serious, well-documented hypersensitivity reaction. However, as noted above, some patients may be successfully switched to a different product. (See 'Choice of IV formulation' above.)

- We warn patients (and infusion personnel) in advance of the infusion that they may experience self-limiting fever, arthralgias, and myalgias, either during the infusion or within 24 hours, and that this does not represent an allergic reaction or cause for panic [76].

- We avoid premedications for patients without asthma or multiple drug allergies. For individuals with asthma or multiple drug allergies, we generally limit premedication to a glucocorticoid alone or with an H2 blocker such as ranitidine or famotidine (methylprednisolone, 125 mg intravenously plus ranitidine 50 mg or famotidine 20 mg intravenously). (See 'Use of premedication' above.)

- For patients with a history of inflammatory arthritis, we administer methylprednisolone, 125 mg intravenously, and prescribe a short course of prednisone (1 mg/kg per day orally for four days) [76].

- We generally limit interventions to minor reactions to temporarily stopping the infusion until the symptoms abate. (See 'Treatment' below.)

There are no immediately available clinical parameters that can unequivocally distinguish between an infusion reaction (non-allergic, often rate-related) and an allergic/anaphylactic reaction, and the vast majority of publications have been unable to definitively distinguish between these reactions. In most cases, treatment may be the same, involving stopping the drug with close observation for minor reactions and aggressive interventions for life-threatening reactions (see 'Treatment' below). While it is prudent to take all reactions seriously, we believe most reactions are due to infusional symptoms (rather than a true allergy) and should be managed as such.

When the above tenets are followed (and the use of HMW ID is avoided), serious adverse events with IV iron are extremely rare, with an estimated frequency of less than 1:200,000. Information about the frequency of infusional and allergic reactions associated with IV iron has been evaluated in the following studies:

- A 2015 review retrospectively compared rates of anaphylaxis among 688,183 individuals who received an IV iron product while enrolled in the United States Medicare program (a large section of the United States population, typically ≥65 years of age) [131]. Overall risks of anaphylaxis were low (range, 24 to 68 cases per 100,000 individuals [0.024 to 0.068 percent]), and some deaths were recorded. However, we believe this may overestimate the frequency of serious reactions because the criteria for anaphylaxis were based on medical coding data that did not allow the investigators to determine whether administration of an antihistamine and wheezing preceded or followed iron administration [132]. This study found rates of anaphylaxis to be higher with ID than other products; however, the rates with ID may also be an overestimate as they included the HMW ID that is known to have a higher risk of adverse reactions and is no longer used. Further, these results may not be directly applicable to a younger population.

- A 2015 systematic review and meta-analysis that included 103 randomized trials of IV iron versus another comparator (eg, oral iron, placebo) found no increased risk of serious adverse events attributable to IV iron (relative risk [RR] 1.04; 95% CI 0.93-1.17) [133]. There were no deaths or anaphylactic reactions in over 10,000 patients who received IV iron. However, severe infusion reactions were more common with IV iron than comparators (RR 2.47; 95% CI 1.43-4.28). As expected, gastrointestinal side effects were lower with IV iron.

- Case reports have described life-threatening adverse events for all of the available IV iron preparations [84,134,135]. True allergic reactions to IV iron products (with documented increases in mast cell tryptase) also have been reported [136,137]. However, we believe these are exceedingly rare and comparable to the incidence of severe allergic reactions to many commonly used medications. As noted above, we have measured tryptase levels in patients who have had infusion reactions with LMW ID and ferumoxytol, and we have found these levels not to be elevated [31].

We consider the US Food and Drug Administration's Adverse Event Reporting System (AERS) a valuable resource for reporting suspected allergic/anaphylactic reactions, but conclusions about absolute risks and/or relative risks among products should not be inferred from the AERS database or other voluntarily submitted reports [84,134,138,139].

**Treatment** — All clinicians administering IV iron should have adequate personnel, training, and equipment to manage extremely rare but potentially life-threatening adverse events, including medications to treat anaphylaxis, resuscitation equipment, and provisions for intensive care management. For the overwhelming majority of patients receiving IV iron, these resources will never be used.

Our approach to managing adverse reactions, should they occur, includes the following [1,69,77,123]:

- Transient fever, arthralgias, myalgias, or flushing are generally seen in approximately 0.5 to 1 percent of infusions. For patients who develop these symptoms **without** associated hypotension, tachypnea, tachycardia, wheezing, stridor, or periorbital edema, we temporarily hold the infusion and observe the patient.

    - We do **not** administer antihistamines or other medications, as these may worsen rather than improve symptoms.
    - If symptoms resolve, we resume and complete the infusion (most common outcome).
    - If symptoms worsen, we treat as a more serious reaction.
    - If symptoms persist unchanged, we may administer a dose of intravenous methylprednisolone, wait 30 minutes, and reinitiate the iron infusion; a short course of oral methylprednisolone also may be administered.
    - Patients are informed that should they develop these symptoms after leaving the infusion facility, they may derive benefit with nonsteroidal anti-inflammatory drugs (NSAIDs), as long as these are clinically appropriate.

- For patients with more serious or true anaphylactic reactions, we treat according to standard protocols. (See "Anaphylaxis: Emergency treatment".)

- For patients with inflammatory arthritis who experience a disease flare, we administer methylprednisolone, 125 mg intravenously, and prescribe a short course of prednisone (1 mg/kg per day orally for four days).

These guidelines are summarized in the table ( table 8).

**Risk of infection** — Bacteria and other infectious agents require iron as a growth factor, and patients with hereditary hemochromatosis and iron overload are known to be at increased risk for certain serious bacterial infections [140]. These observations have suggested that the use of therapeutic doses of iron might be associated with an increased risk of infection.

We believe the risk of infection with IV iron administration is negligible. This is supported by a 2015 meta-analysis of trials comparing outcomes with IV iron versus controls including oral iron, intramuscular iron, placebo, or no iron (RR 1.17; 95% CI 0.83-1.65) [133]. A 2013 meta-analysis of this subject found a slightly increased risk of infection with IV iron compared with oral iron (RR 1.33; 95% CI 1.10-1.64), but it was acknowledged that information on the risk of infection was available in only 24 of the 72 studies, and missing data could have created bias [65]. Additionally, there was no dose-response association between iron and infectious risk, and rates of mortality and other serious adverse events were not increased with IV iron treatment. Additional trials and observational studies in specific patient populations also have not demonstrated increased infectious risks [98,101,141-144].

As noted above, we delay IV iron administration in patients with active infection until the infection is resolved. (See 'Uses for IV iron' above.)

**Routes we do not use (IM, transdermal)** — In contrast to oral and IV iron, we do not use other routes of administration.

- **Intramuscular** – Intramuscular (IM) iron is available and will raise the iron level, but this route of administration is painful, stains the buttocks, and has variable absorption [123]. Case reports have also described development of sarcoma following IM iron administration [145,146].

- **Transdermal** – Transdermal iron delivery systems are being studied in animal models [147]. However, there is no clinical evidence in humans that the transdermal route is effective or safe.

## RESPONSE TO IRON SUPPLEMENTATION

**Typical response** — An effective regimen for the treatment of uncomplicated iron deficiency with oral iron preparations should lead to the following responses:

- If pagophagia (pica for ice) is present, it often disappears almost as soon as oral or intravenous (IV) iron therapy is begun, well before there are any observable hematologic changes such as reticulocyte response. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Pica and ice craving'.)

- The patient will note an improved feeling of well-being within the first few days of treatment.

- If restless legs syndrome accompanies documented iron deficiency, the overwhelming majority will experience complete or near complete relief within 72 hours of the infusion, often on the first night thereafter.

- In patients with moderate to severe anemia, a modest reticulocytosis will be seen, peaking in approximately 7 to 10 days. Patients with mild anemia may have little or no reticulocytosis.

- The hemoglobin concentration will rise slowly, usually beginning after approximately one to two weeks of treatment, and will rise approximately 2 g/dL over the ensuing three weeks. The hemoglobin deficit should be halved by approximately one month, and the hemoglobin level should return to normal by six to eight weeks.

- Measures of iron stores will improve, including serum ferritin and transferrin saturation (TSAT). (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Iron studies (list of available tests)'.)

- Typically, papillation of the tongue is decreased in patients with iron deficiency and can be used as a gauge of duration of symptoms. Classically, loss of papillae begins at the tip and lateral borders and moves posteriorly and centrally. Following iron repletion, a rapid correction (weeks to months) is observed.

**Monitoring and hemoglobin/iron targets** — Monitoring of patients receiving iron replacement depends on the severity of anemia.

For patients receiving oral iron, we often re-evaluate the patient two weeks after starting. We check the hemoglobin and reticulocyte count and review tolerability of the oral iron. For IV iron, we generally see patients four to eight weeks after the iron has been administered. We do not obtain repeat iron parameters for at least four weeks, because IV iron interferes with most assays of iron status [148].

If an individual has ongoing loss of iron (from chronic bleeding), management should focus on treating the bleeding rather than attempting to compensate for bleeding by providing chronic iron therapy. However, there may be instances when ongoing blood loss cannot be fully treated (eg, hereditary hemorrhagic telangiectasia, abnormal uterine bleeding), and these individuals may require frequent visits to establish an effective iron dose and teach the patient how to monitor ongoing blood loss. If these individuals tolerate oral iron, it is reasonable to take one tablet every other day or twice weekly; however, if there is a condition in which oral iron is ineffective or harmful (after gastric bypass surgery; in inflammatory bowel disease) or prior intolerance, we do not use maintenance oral iron. (See "Hereditary hemorrhagic telangiectasia (HHT): Evaluation and therapy for specific vascular lesions", section on 'Iron deficiency and iron deficiency anemia' and "Abnormal uterine bleeding: Management in premenopausal patients".)

Iron is generally given until levels of ferritin and transferrin saturation normalize. Some individuals may require higher-than-average iron stores, such as a person with gastrointestinal telangiectasias who has frequent gastrointestinal bleeding. When ferritin and transferrin saturation are discordant, we place greater emphasis on the transferrin saturation (TSAT). Ferritin is an acute phase reactant and may be chronically elevated in individuals with concomitant inflammatory processes even when iron stores are low. Another option for monitoring that is under study is the reticulocyte hemoglobin (CHr) [149]; this may also facilitate monitoring the response to treatment and assessment of the need for additional iron therapy. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Diagnostic evaluation'.)

Total body iron stores in adults are generally in the range of 5 mg/kg in women and 10 mg/kg in men. Thus, correction of anemia plus repletion of iron stores may require up to a gram or more of elemental iron. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Normal body iron content'.)

As noted above, a normal healthy diet contains sufficient iron for physiologic needs. (See 'Role of diet' above.)

**Approaches to lack of response** — On occasion, a patient's hemoglobin level and iron stores may not normalize with iron supplementation. There are a number of potential causes for this situation ( table 9):

- Patient not taking oral iron (eg, due to side effects) (see 'Side effects (oral iron)' above)
- Reduced absorption of oral iron (see 'Dosing and administration (oral iron)' above)
- Blood loss exceeds iron intake
- Incorrect initial diagnosis
- More than one diagnosis (especially relevant in older adults)
- Inflammatory state with block in intestinal iron regulation ( figure 1)
- Therapy was effective but bleeding recurred

For those who are taking the iron supplement and do not have an obvious explanation for lack of an increase in hemoglobin level and iron stores, it may be prudent to screen for celiac disease, autoimmune gastritis, and/or *H. pylori* infection, all of which have been implicated in reduced oral iron absorption. It has been reported that over half of patients with unexplained iron deficiency anemia are infected with *H. pylori*, and patients with *H. pylori* infection have a pooled odds ratio of iron deficiency of 2.8 compared with uninfected individuals [150]. In a series of 150 patients with unexplained iron deficiency anemia, there were eight newly diagnosed cases of adult celiac disease (5 percent); 40 cases (27 percent) of autoimmune gastritis, 22 of which were associated with previously undetected vitamin B12 deficiency (27 and 15 percent, respectively); and 77 cases of *H. pylori* infection, 29 of which had *H. pylori* as the sole abnormality detected (55 and 19 percent, respectively) [151]. Of 26 evaluable *H. pylori*-positive patients who had successful *H. pylori* eradication followed by administration of oral iron, 19 (73 percent) had a response, with mean increase in hemoglobin from 9.4 mg/dL to 13.5 mg/dL.

Celiac disease in particular has additional management implications if present. (See "Diagnosis of celiac disease in children" and "Diagnosis of celiac disease in adults" and "Indications and diagnostic tests for Helicobacter pylori infection in adults".)

Some individuals whose anemia does not respond to oral iron due to an inflammatory block may benefit from IV iron. This has been demonstrated in various trials in various populations. As examples:

- A series of 812 patients with iron deficiency who were unable to tolerate oral iron or whose hemoglobin did not increase with oral iron were randomly assigned to receive IV iron (ferumoxytol, two 510 mg doses one week

apart) versus placebo [91]. Compared with placebo, patients who received IV iron were more likely to have an increase in hemoglobin of ≥2 g/dL at week 5 (6 versus 81 percent). Other endpoints such as hemoglobin ≥12 g/dL and functional fatigue score also favored the IV iron arm.

- A series of 240 iron-deficient patients who participated in a trial that stratified them according to initial response to oral iron at two weeks [47]. Compared with responders, nonresponders had higher hepcidin levels (11 versus 38 ng/mL). In a subset of 45 nonresponders randomly assigned to receive additional oral iron or IV iron (ferric carboxymaltose [FCM]), FCM was more effective at increasing hemoglobin levels (hemoglobin increase of ≥1 g/dL in 65 versus 21 percent).

Other individuals may have additional diagnoses, either initially misdiagnosed as iron deficiency, concomitant with iron deficiency, or rarely, developing during treatment of iron deficiency. Examples include nutrient deficiencies (vitamin B12, folate, copper), bone marrow abnormalities (myelodysplastic syndrome), inherited anemias (thalassemia, enzyme defects), hypothyroidism, other genetic conditions that affect iron balance such as iron-resistant iron deficiency anemia (IRIDA), and disorders associated with chronic inflammation. Investigation for these (indications and appropriate testing) is discussed in separate topic reviews. The specific sequence and extent of testing for causes of lack of response is guided by the patient's family history, medical history, and physical examination. (See "Diagnostic approach to anemia in adults" and "Anemia of chronic disease/anemia of inflammation" and "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Inherited disorders/IRIDA'.)

## 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 5$^{th}$ to 6$^{th}$ 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 10$^{th}$ to 12$^{th}$ 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

- **Whom to treat** – Regardless of the presence of symptoms, all patients with iron deficiency anemia and most patients with iron deficiency without anemia should be treated. The cause of iron deficiency also must be identified and addressed, especially in adults with new onset iron deficiency. A healthy diet provides sufficient iron for physiologic needs but cannot correct iron deficiency. (See 'Initial considerations' above.)

- **Role of RBC transfusion** – Patients with severe, severely symptomatic (eg, with symptoms of myocardial ischemia), or life-threatening anemia should be treated with red blood cell (RBC) transfusion ( algorithm 1). (See 'Severe/life-threatening anemia' above.)

- **Oral versus IV iron** – Some conditions may affect iron dosing and/or the route of administration (oral versus intravenous [IV]) ( table 2). We generally treat patients who have uncomplicated iron deficiency anemia with oral iron due to the ease of administration, as illustrated in the algorithm ( algorithm 1). However, the availability of IV iron formulations with improved toxicity profiles has lowered the threshold at which many patients would prefer an IV preparation. We often use IV iron when treating pregnant women and individuals with inflammatory bowel disease, gastric surgery, or chronic kidney disease. (See 'Oral versus IV iron' above and "Anemia in pregnancy" and 'Older adults' above and 'Inflammatory bowel disease' above and 'Following gastrointestinal/bariatric surgery' above and 'Perioperative' above and 'Chronic kidney disease' above and 'Heart failure' above and 'H. pylori, peptic ulcer disease, and gastritis' above.)

  - **Dose and formulation (oral iron)** – For the most part, all oral iron preparations are equally effective ( table 4). The dose of oral iron depends on patient age, the estimated iron deficit, the rapidity with which it needs to be corrected, and side effects, which include metallic taste, and a number of gastrointestinal effects that generally correlate with dose. For individuals treated with oral iron, we suggest that the dose be taken every other day rather than every day (**Grade 2C**). This is based on evidence in individuals with iron deficiency that demonstrates improved absorption and reduced gastrointestinal side effects. Some individuals may reasonably choose daily dosing if they find that it improves tolerability or ease of use. Other strategies to improve tolerability are listed above. (See 'Oral iron' above.)

  - **Dose and formulation (IV iron)** – There are a number of settings in which IV may be preferable to oral administration, including ongoing blood loss, physiologic or anatomic abnormality that interferes with oral absorption or iron homeostasis, and intolerable gastrointestinal side effects of oral iron. A number of IV iron formulations are available ( table 3); their dosing and administration are described above. (See 'Choice of IV formulation' above and 'Dosing/administration of specific IV iron preparations' above.)

- **Adverse effects of oral iron** – Gastrointestinal side effects are extremely common with oral iron administration. Strategies to reduce these effects include reducing the frequency to every other day if not done already, dietary modifications, and switching to a liquid formulation. (See 'Side effects (oral iron)' above and 'Strategies to improve tolerability' above.)

- **Adverse effects of IV iron** – Many clinicians are reluctant to use IV iron due to concerns about anaphylaxis. We believe true allergic reactions are exceedingly rare and vastly overestimated, largely due to experience with older products such as high molecular weight iron dextran (HMW ID), which is no longer used, and the practice of aggressively treating non-allergic infusion reactions with diphenhydramine and other therapies that convert the reaction to a more serious event. We do not use routine premedication prior to IV iron and we avoid diphenhydramine. For individuals with asthma, inflammatory rheumatic conditions, or multiple drug allergies, we generally limit premedication to a glucocorticoid alone. (See 'Allergic and infusion reactions' above.)

- **Expected response** – Effective treatment of iron deficiency results in resolution of symptoms, a modest reticulocytosis (peaking in 7 to 10 days), and normalization of the hemoglobin level in six to eight weeks. Causes for a lack of response include nonadherence to oral iron, ongoing blood loss, and incorrect initial diagnosis or the presence of additional diagnoses. Some of these additional diagnoses, such as celiac disease, may be especially important to evaluate. (See 'Response to iron supplementation' above.)

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