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Practical Approach to Manage Patient with Iron Deficiency Anemia

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Abstract

Anemia impacts a quarter of the global population, predominantly due to iron deficiency, leading to symptoms such as chronic fatigue, reduced cognitive abilities, and decreased overall well-being. Often, patients with unexplained iron deficiency anemia are directed to gastroenterologists, as gastrointestinal causes are commonly at the root of the problem. Effective management of this condition can significantly enhance life quality, relieve symptoms of iron deficiency, and lower the reliance on blood transfusions. While oral and intravenous iron treatments are available, oral iron's effectiveness may be compromised in gastrointestinal issues like inflammatory bowel disease, celiac disease, and autoimmune gastritis. This article offers a detailed review of diagnosing and treating iron deficiency anemia and proposes a management algorithm to aid clinicians in deciding when further gastrointestinal investigation is necessary. This approach helps in pinpointing and addressing the fundamental issue, thus preventing the needless application of invasive procedures and their related hazards.

Keyword: iron supplementation, dietary iron intake, iron-rich foods, iron absorption, hemoglobin levels.

Pathophysiology

Anemia from iron-limited red blood cell production can happen through various processes. In cases of true iron deficiency, iron stores diminish due to an imbalance in iron absorption and usage. Initially, anemia may not manifest because the body recycles iron from old red blood cells. Yet, patients can experience symptoms like fatigue and restless leg syndrome (RLS) even before anemia develops. Continuous iron deficit leads to anemia characterized by small, pale red blood cells. Correcting iron levels and addressing the underlying cause of deficiency can resolve this issue.[1]

Functional iron deficiency, however, occurs when there's a block in iron's movement into the bloodstream from cells in the gut, liver, or immune system, leading to anemia with normal or small red blood cells despite sufficient iron reserves. This condition underlies the anemia of chronic disease (ACD), where inflammation triggers excess hepcidin production, hindering iron absorption and release. Here, oral iron supplements are usually ineffective, making intravenous iron the treatment of choice. Especially in patients with conditions like inflammatory bowel disease (IBD), where iron shortage and inflammation coexist, this form of anemia requires careful treatment planning.

Table 1: Cause of iron deficiency

	New born	**Low birth weight** **Perinatal blood loss** **Low maternal iron stores**
	Infants, small children	Excessive consumption of cow's milk Inadequate dietary intake Intake of foods that disrupt iron absorption
	Adolescents	Growth spurt Menstrual period Von willebrand disease
	Occult Bleeding	Peptic ulcer Meckel's diverticulum Intestinal polyp Hemangioma
	Insensible Blood loss	Celiac disease Chronic diarrhea Pulmonary hemosiderosis parasitosis

Diagnosis

The World Health Organization defines anemia as hemoglobin (Hb) levels below 13.0 g/dL in adult males, below 12.0 g/dL in non-pregnant adult females, and below 11.0 g/dL in pregnant women. Variations in Hb levels exist across different age groups and races, so careful consideration is needed,[2] especially when interpreting borderline results. Additionally, factors such as smoking, living at higher altitudes, and engaging in endurance sports can influence baseline Hb levels.

Differentiating between macrocytic anemia and iron deficiency anemia, characterized by hypochromic and typically microcytic features, relies on mean corpuscular Hb and mean corpuscular volume. Deficiencies in multiple nutrients or the use of thiopurine medications like azathioprine in conditions such as inflammatory bowel disease (IBD) can lead to a combination of iron deficiency anemia and macrocytosis, resulting in normocytic anemia. In such cases, a high red cell distribution width can help identify the iron deficiency component. Platelet and leukocyte counts aid in ruling out pancytopenia. Consideration of thalassemia traits is also important, particularly in populations where these traits are prevalent, as they present with microcytic, hypochromic anemia.

Transferrin saturation (TfS) and serum ferritin levels are further parameters used to diagnose iron deficiency. A TfS below 20% and ferritin levels lower than 30 ng/mL indicate iron deficiency. However, ferritin levels can be affected by inflammation, necessitating consideration of inflammatory parameters like C-reactive protein. Different cutoff values are applied in the presence of inflammatory conditions such as IBD, chronic kidney disease (CKD), and congestive heart failure (CHF) to diagnose iron deficiency. In cases where diagnosis remains uncertain, soluble transferrin receptor (sTfR) and sTfR/log ferritin index can help distinguish between iron deficiency anemia and anemia of chronic disease (ACD), as sTfR is elevated only in iron deficiency anemia.

Management

There is compelling evidence supporting the timely treatment of iron deficiency anemia as it significantly enhances quality of life, physical well-being, and mitigates symptoms such as fatigue and cognitive impairment. While definitive evidence is lacking, non-anemic iron deficiency has been linked to conditions like restless leg syndrome (RLS) and chronic fatigue, with treatment showing potential in alleviating these symptoms. In cases of congestive heart failure (CHF), iron replacement therapy has demonstrated benefits, even in the absence of anemia. Therefore, the decision to initiate iron deficiency treatment in non-anemic individuals should be made on a case-by-case basis. For patients with conditions like chronic kidney disease (CKD), CHF, or cancer, iron deficiency anemia management should involve collaboration with relevant specialists due to varying treatment guidelines.

Oral Iron

Intestinal absorption of iron is limited, with maximum absorption rates of oral iron reaching 20% to 25%, typically observed in the late stages of iron deficiency. In latent iron deficiency and iron deficiency anemia, absorption rates correspond to around 10% and 13%, respectively, compared to approximately 5% in healthy males and 5.6% in healthy females. Excess iron remaining in the intestinal lumen can lead to mucosal injury, with animal studies suggesting potential exacerbation of disease activity and induction of carcinogenesis in inflammatory bowel disease (IBD). Additionally, gastrointestinal side effects, which are dose-dependent, can impede compliance, with up to 50% of patients experiencing nonadherence. Therefore, adjusting dosage to enhance tolerability is reasonable. While typical doses range from 100 to 200 mg of elemental iron per day, effective repletion can be achieved with lower doses, ranging from 15 to 30 mg of elemental iron daily. Various over-the-counter formulations, mainly composed of ferrous iron salts like ferrous sulfate, ferrous gluconate, and ferrous fumarate, are available.

Oral iron supplementation is effective when intestinal uptake functions properly. However, its use should be restricted to patients with mild anemia (hemoglobin levels between 11.0-11.9 g/dL in non-pregnant women and 11.0-12.9 g/dL in men) due to its slow repletion rate.[3] When faster repletion is desired, intravenous administration is preferred, although oral iron remains a convenient and cost-effective option.

Table 2: oral vs intravenous Iron

	pros	**cons**
Oral iron	Available over the counter Convenient Inexpensive Effective when intestinal absorption is not impaired	Limited daily intestinal absorption results in slower iron repletion. Dose-dependent gastrointestinal side effects (nausea, vomiting, abdominal pain, constipation) may limit patient compliance. Uptake is impaired in the setting of disease (eg, celiac disease, anemia of chronic disease, autoimmune gastritis). Mucosal injury and/or potential exacerbation of disease activity may occur in inflammatory bowel disease. Alteration of microbiota and tumorigenic potential have been observed.[a]

Intravenous iron	Fast repletion of iron stores Safe if formulations with dextran are avoided Effective even when intestinal absorption is impaired	Requires administration by a health care professional, with associated increased costs Potential for iron overload and transient increase in oxidative stress Potential for anaphylactic reactions with dextran-containing formulations

Intravenous iron

Intravenous iron therapy is highly effective in treating iron deficiency anemia, particularly when oral iron proves ineffective. Oral iron's efficacy diminishes when gut absorption is compromised (as seen in conditions like celiac disease, autoimmune gastritis, anemia of chronic disease, or post-gastric or duodenal surgery), or when there are significant and ongoing iron losses (such as in menorrhagia, gastrointestinal bleeding, or post-surgery situations). Additionally, patient compliance with oral iron may be hindered by side effects, further limiting its effectiveness. In such cases, intravenous iron therapy is preferred as it bypasses the gut, leading to faster repletion of iron stores. Intravenous administration also results in a quicker increase in ferritin levels compared to oral iron, reducing the risk of recurrent iron deficiency anemia over time.

However, there are drawbacks to intravenous iron therapy, notably the need for administration by a healthcare professional, which adds to the associated costs. Safety concerns were previously raised, especially with high-molecular-weight iron dextran (HMWID), which led to apprehensions about all intravenous formulations. Yet, a review of adverse events showed low rates, particularly for low-molecular-weight iron dextran,[4] iron sucrose, and ferric gluconate, excluding HMWID. Ferric carboxymaltose demonstrated similar efficacy to HMWID with fewer hypersensitivity reactions. While direct comparisons among intravenous formulations are limited, it is generally recommended to avoid HMWID due to potential anaphylactic risks. HMWID has been discontinued in the United States and Europe. All dextran-containing compounds require a test dose, and if there's a known sensitivity to dextran, a test dose is also prudent for iron sucrose and iron gluconate.

Table 3: intravenous iron preparation

Iron Formulation	Test dose	Dose Per Session
High molecular weight iron dextran	25mg (0.5mL) over 5 mints, monitor 1 hr	100mg of iron IV at <50mg/min
Low molecular weight iron dextran	25mg (0.5mL) over 30 sec, monitor 1 hr	100mg of iron IV at <50mg/min
Ferric Carboxymaltose	No	750mg of iron IV at 100mg/min or infusion over 15 mint. For patients weighing <50 kg (110lb), max of 15 mg of iron per kg of body weight.
Ferumoxytol	No	510mg of iron IV at 30mg/s or infusion over 15 mint.
Iron sucrose	No	100-150 mg IV over 2-5 mints or infusion over 15 mints.
Sodium ferric Gluconate complex	No	62.5-12.5 mg IV over 12.5 mg/mint or infusion over 1 hour.

Blood transfusion

Blood transfusions should be used sparingly in cases of chronic iron deficiency anemia. They may be considered for patients with active bleeding who are hemodynamically unstable, or for those with critical anemia (Hb level <7 g/dL), acute myocardial ischemia, or if other treatments fail to correct the anemia. For patients with significant cardiovascular disease, higher cutoff values (Hb <8 g/dL) may be appropriate. However, transfusions are only a temporary solution, and efforts should focus on identifying and treating the underlying cause of anemia. Intravenous iron therapy, along with erythropoiesis-stimulating agents if necessary, should be administered concurrently to correct and maintain hemoglobin levels and iron stores, thereby reducing the need for future transfusions.

Long-term Consideration in the management of iron deficiency

Iron deficiency and thrombosis

Iron deficiency is associated with reactive thrombocytosis, although the exact mechanism remains unclear. Studies in adult women reveal a correlation between platelet count and transferrin saturation (TfS) and serum iron, with more severe anemia leading to higher platelet counts. Animal models of iron

deficiency replicate this observation, demonstrating alterations in megakaryopoiesis and increased platelet aggregability. Patients with iron deficiency also exhibit altered platelet function, which is improved with iron therapy.

Both pediatric and adult studies, particularly in women, indicate an association between stroke and iron deficiency anemia. Those with pulmonary arteriovenous malformations face a higher risk of ischemic strokes, with low serum iron doubling this risk. Cancer and inflammatory bowel disease (IBD) are conditions associated with anemia and increased risk of venous thromboembolism, often accompanied by thrombocytosis. Iron therapy in IBD normalizes platelet counts and function, while in chronic kidney disease (CKD), it lowers platelet counts. In cancer, concurrent administration of intravenous iron and an erythropoiesis-stimulating agent reduces the incidence of venous thromboembolism more effectively than the use of an erythropoiesis-stimulating agent alone. Overall, these findings suggest that proper iron management has the potential to decrease the occurrence of thromboembolic events by reducing both platelet number and activity.

Iron therapy and carcinogenesis

Iron homeostasis is intricately regulated to balance the need for erythropoiesis and cellular function with the potential harm of free iron-induced redox damage. Fe(II) iron, when reacting with hydrogen peroxide, can produce highly reactive hydroxyl radicals, causing damage to biomolecules and posing a concern for potential tumor promotion or progression during iron therapy.

NHANES studies have indicated that a high transferrin saturation (TfS) and elevated iron intake together increase the risk of cancer. Conversely, the Swedish AMORIS study found a positive association between total iron-binding capacity (which rises with low available iron) and cancer risk. Population studies have reported an association between high red meat consumption and increased colorectal cancer risk, although results vary by gender, potentially influenced by factors like geographic differences, disease prevalence, and iron deficiency rates.

Clinical and animal studies involving oral iron (mainly ferrous sulfate) and intravenous iron (primarily iron sucrose and iron gluconate) demonstrate increased oxidative stress markers in various organ systems. The induction of oxidative stress depends on the amount of free redox-active iron, influenced by drug pharmacokinetics. Intravenous iron compounds differ in stability, with less stable complexes dissociating in circulation, while more stable complexes remain intact until breakdown in the endolysosome. Potential alternative oral iron compounds, combining purportedly less reactive Fe(III) iron with a complex to enhance bioavailability (such as Fe(III) hydroxide-polymaltose and ferric maltol), have been investigated.

Regrettably, there is limited research directly comparing medications, and the potential long-term effects of iron therapy on carcinogenesis remain uncertain, as reviewed by Beguin and colleagues. However, ensuring the proper and judicious administration of iron should mitigate the risk of excessive iron supply, particularly in cases of iron deficiency anemia.

Conclusion

Anemia is widespread in both the general populace and clinical settings, significantly impacting quality of life, clinical outcomes, and healthcare expenses. Iron deficiency stands as the primary cause, and even in the absence of anemia, iron deficiency alone can lead to symptoms such as fatigue, restless leg syndrome (RLS), and cognitive impairment. Treatment of iron deficiency anemia is imperative upon diagnosis, and symptomatic iron deficiency without anemia should also be considered for treatment. Gastroenterologists have taken on a pivotal role in managing patients with intestinal bleeding or iron malabsorption. They possess expertise in conducting endoscopic procedures for diagnostic and therapeutic purposes and should likewise excel in administering intravenous iron replacement therapy when necessary.

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