

Approach to the Iron Deficient Patient

Summary

- Determine if the patient has absolute iron deficiency, functional iron deficiency or both for decisions related to effective management.
- Reticulocyte studies are always indicated when assessing / diagnosing iron deficiency.
- Iron studies should consist of serum iron, total iron binding capacity (TIBC), percent transferrin saturation (Fe/TIBC) and serum ferritin should suffice to diagnose iron deficiency.
- Iron therapy choice should be based on patient's iron status, tolerance of oral iron and urgency of correction.

Introduction

In this attempt to forge a useful algorithm for the management of iron deficiency, it is prudent to have a discussion of the difference between **absolute (overt)** iron deficiency and **functional** iron deficiency.

Overt Iron Deficiency ^{1,2}

Body iron stores are depleted.

Absolute, or overt iron deficiency, is due to iron loss from bleeding, or iron absorption that falls short of daily losses. The most common causes of iron deficiency due to blood loss include gastrointestinal (including both upper and lower gastrointestinal blood loss) and genitourinary blood loss (including menstrual blood loss).

In the western world, iron loss deficiency due to bleeding is, by far, more common. Inadequate iron intake is rare due to fortification of many prepared foods with iron. However, iron deficiency due to decreased uptake or absorption may be seen in malabsorption syndromes such as untreated celiac disease and in unusual diets and with the introduction of cow's milk, rather than formula, in infants younger than 12 months of age.

It is absolutely imperative that the healthcare provider treating iron deficiency meticulously search for sources of blood loss to avoid missing potentially treatable life threatening illnesses.

Functional Iron Deficiency ^{1,2}

(also known as iron restricted erythropoiesis)

Ample iron is present, but with reduced bioavailability.

Central to this process is hepcidin, an iron regulatory protein synthesized by the liver that blocks iron absorption by binding to and inactivating the membrane-bound, iron transport protein, ferroportin, in intestinal erythrocytes and reduces release of iron from macrophages.³ Hepcidin is upregulated in a large variety of inflammatory disease states, resulting in anemia due to a reduction in the bioavailability of iron to support normal erythropoiesis. Prior to the discovery of hepcidin, the hepatic synthesized iron regulatory protein, functional iron deficiency was referred to as anemia of chronic disease or anemia of chronic inflammation.

Laboratory Profile of Anemia:

Iron Deficiency Anemia (IDA) vs. Functional Iron Deficiency (FID) vs. Combined Anemia

Test	IDA	FID	IDA + FID
Iron	Low	Low	Low
Ferritin	Low	Normal-High	Low-Normal
Transferrin	High	Low-Normal	Low
Transferrin saturation	Low	Low	Low

⁴Adapted from Weiss G, Goodnough LT. *N Engl J Med* 2005; 352:1011-1023

Diagnosis of Iron Deficiency

What Laboratory Tests are Needed?⁵

Absolute Reticulocyte Count

Both overt and functional iron deficiency are associated with decreased red cell production, manifested by reticulocytopenia. The measurement of the reticulocyte count is therefore always indicated.

For practical purposes, an absolute reticulocyte count of <75,000 in the presence of a decreased hemoglobin represents hypoproliferation (or decreased red cell production). Once increased destruction is excluded, confirmatory tests for iron deficiency should be done.

Reticulocyte Index

A convenient way to assess bone marrow response to anemia is through the reticulocyte index. A value <2 suggests a response to anemia is insufficient; a value >3 suggests an adequate response.⁶

Reticulocyte Hemoglobin Content (CHr, MCHr, RET-He)

Reticulocyte hemoglobin content is a direct measure of iron in the reticulocyte measured in picograms (pg). A mean CHr less than 28 pg is strongly suggestive of iron deficient erythropoiesis

Iron Status Tests

In an otherwise healthy patient (without concomitant co-morbidities), a serum iron, total iron binding capacity (TIBC), percent transferrin saturation (Fe/TIBC) and serum ferritin should suffice to diagnose iron deficiency and be strongly indicative of functional iron deficiency in the context of the patient's clinical history. If the ferritin is elevated in the face of decreased percent transferrin saturation, a C-reactive protein as an indicator of inflammation may be useful in demonstrating that a normal or elevated ferritin is due to inflammation rather than normal iron stores.

Mean Corpuscular Volume (MCV)

The MCV can be helpful as well; however, the test lacks both sensitivity and specificity. Many patients with iron deficiency, both overt and functional, may have a normal MCV while a decreased MCV may be

seen with certain hemoglobinopathies, e.g. thalassemia.

When Should Labs be Drawn?

These tests are best done fasting. There is a diurnal variation of iron levels and recent food intake can markedly affect the serum iron level, that, in turn, affects the transferrin saturation.

Symptomatic Diagnosis

If long standing iron deficiency is suspected, a simple question about ice craving (pagophagia) can be a useful screening assessment for iron deficiency. Classical physical findings include a glasslike tongue and ridged fingernails (Mees' lines).

For more information, go to: [Laboratory Studies in the Diagnosis of Iron Deficiency, Latent Iron Deficiency and Iron Deficient Erythropoiesis](#)

Management of Absolute Iron Deficiency

Oral Iron Therapy

Consideration of oral iron remains the standard of care for the initial treatment of uncomplicated iron deficiency. A variety of enteric iron preparations are available without prescription but have been shown to vary in gastrointestinal tolerability. Listed in order of DECREASING adverse event percentage: Ferrous fumarate, ferrous sulfate, ferrous gluconate, ferrous glycine sulfate, iron protein succinylate and ferrous sulfate mucoprotease.⁷ Efficacy is probably equivalent.

Clinicians learn during training that oral iron is *well tolerated*. However, many patients complain of mild to significant adverse events and are not able to continue oral iron therapy.⁷

These adverse events include:⁷

- stomach cramping
- constipation or diarrhea
- constant metallic taste
- nausea
- sticky stool that is green and malodorous
- abdominal bloating

Recent studies suggest that alternative day oral iron supplementation may improve iron uptake, while also reducing the side effects.⁸

Compared to intravenous iron, oral iron is far less efficacious, takes considerably longer to work, and is ineffective in the presence of:⁹

- chronic diseases such as inflammatory bowel disease and other inflammatory processes
- chronic renal failure
- malabsorption disorders
- malignancies

Enteric iron replacement may be inadequate, even if tolerated, if the rate of blood loss, and therefore iron loss, exceeds the patient's maximum rate of daily iron absorption with optimal oral iron replacement.⁹ This may be seen due to a reduction in iron absorption secondary to bariatric surgery or malabsorption, or significant chronic blood loss such as from gastrointestinal pathology or dysfunctional uterine bleeding.

Oral iron is contraindicated in inflammatory bowel disease where it is directly toxic to the intestinal endothelium exacerbating the inflammation.

Intravenous (IV) Iron Therapy

IV iron therapy is indicated for any patient in whom enteric iron replacement is ineffective or not tolerated. In addition, since the response to parenteral iron is much faster, clinical circumstances such as an urgent need for surgery, might dictate the medical necessity of intravenous iron. There are currently five IV iron preparations available in the US.

For more information, go to [Treatment of Iron Deficiency Anemia](#)

References

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