

Approach to the Iron Deficient Patient

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 **overt** iron deficiency and **functional** iron deficiency.

Overt Iron Deficiency^{1,2}

Body iron stores are depleted

- True, or overt iron deficiency, is due to iron loss from bleeding.
- In the western world there is no other cause. Even if one wishes to postulate that severe nutritional iron lack could theoretically lead to iron deficiency, since flour is fortified with iron, it is likely that starvation would ensue prior to clinically significant iron deficiency based on poor intake.
- Therefore, although not the topic of this document, it is absolutely imperative that the healthcare provider treating the 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 unavailable

- Prior to the discovery of hepcidin, the hepatic synthesized iron regulatory protein, functional iron deficiency was referred to as anemia of chronic disease.
- It is now known that hepcidin blocks iron absorption by inactivating the only known iron exporter, ferroportin in intestinal enterocytes.
- Hepcidin also blocks iron release from circulating macrophages by inactivating ferroportin in these cells as well. Since hepcidin is upregulated in a huge variety of disease states, anemia of chronic disease occurs due to iron lack.

Laboratory Profile of Anemia:

Iron Deficiency Anemia vs. Anemia of Chronic Disease vs. Combined Anemia

Test	IDA	ACD	IDA + ACD
Iron	Low	Low	Low
Ferritin	Low	Normal-High	Low-Normal
Transferrin	High	Low-Normal	Low
Transferrin saturation	Low	Low	Low
Soluble transferrin receptor	High	Normal	Normal-High
Cytokine levels	Normal	High	High

³Adapted from Weiss G, Goodnough LT. *N Engl J Med* 2005; 352:1011-1023

Diagnosis of Iron Deficiency

What laboratory tests are needed?⁴

Absolute Reticulocyte Count

Both overt and functional iron deficiency are associated with decreased red cell production, which is 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.

Iron Status Tests

In an otherwise healthy patient (without concomitant comorbidities), a serum iron, total iron binding capacity (TIBC), percent transferrin saturation (Fe/TIBC) and serum ferritin should suffice.

Mean Corpuscular Volume (MCV)

The MCV can be helpful as well; however, since the hemoglobin falls prior to the MCV, iron deficiency anemia is often normochromic. Further, at least 30% of anemias of chronic disease have microcytosis. As the deficiency becomes more severe, microcytosis and

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hypochromia ensue. Therefore, the MCV is only inferential and not confirmatory.

When should labs be drawn?

It should be noted that these tests should be done fasting. There is a diurnal variation of iron levels and recent food intake can markedly affect the serum iron level, which in turn affects the transferrin saturation.

Symptomatic Diagnosis

If long standing iron deficiency is suspected, a simple question about ice craving (pagophagia) can be diagnostic. Lastly, classical physical findings include a glasslike tongue and ridged fingernails (Mees' lines).

For more information visit: Laboratory Studies in the Diagnosis of Iron Deficiency, Latent Iron Deficiency and Iron Deficient Erythropoiesis

Management of Absolute Iron Deficiency

The most common causes include women with menorrhagia or pregnancy, those with acute blood loss from benign conditions such as peptic or gastric ulcers and those with uncomplicated surgical blood loss.

Oral Iron Therapy

Oral iron remains the standard of care for the initial treatment of uncomplicated iron deficiency. Ferrous sulfate is the most effective oral iron. Many other oral iron preparations are available, but none has been shown to be more effective and less toxic than ferrous sulfate. There are preparations such as timed-release iron and enteric-coated iron. While these preparations are less toxic, they are also ineffective.⁵

Clinicians learn that oral iron is *well tolerated* during training. Although it certainly is well tolerated in some patients, the overwhelming majority of patients complain of mild to significant adverse events.⁵

These include⁶:

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

Compared to intravenous iron, oral iron is far less efficacious, takes considerably longer to work, and is ineffective in the presence of⁶:

- chronic diseases such as collagen vascular disease
- chronic renal failure
- malabsorption disorders
- malignancies

Oral iron is also ineffective in a whole host of disorders associated with chronic blood loss, where the oral iron simply cannot keep up with the blood loss. These disorders include⁶:

- AV malformations of the intestine
- Angiodysplasia - common in diseases with small vessel pathology like diabetes, patients who have undergone bariatric surgery; Hereditary hemorrhagic telangiectasias (Osler-Weber-Rendu).

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

For more information please visit: Treatment options: Oral Iron

IV Iron Therapy

For any patient with any disorder where oral iron is unable or unlikely to work, IV iron is administered. There are currently six IV iron preparations available in the US. These include:

- high and low molecular weight iron dextran (HMW and LMW ID)
- ferric gluconate (FG)
- iron sucrose (IS)
- ferumoxytol
- iron carboxymaltose

For more information please visit: Treatment options: IV Iron

References

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