Guidelines for the Use of Laboratory Tests for Iron Deficiency (CLP 002)

Revised July 2024

1. Purpose

To provide clinicians with a concise reference document describing the appropriate laboratory tests for assessing patients of all ages suspected of having iron deficiency. The guidelines in this document are in alignment with the Raise the Bar campaign, which was developed to increase awareness of the high prevalence of iron deficiency, particularly in women, and to improve the diagnosis and treatment of this correctable disorder.[1] The Raise the Bar website is found here and provides additional information on diagnosis and treatment of iron deficiency and iron deficiency anemia: https://www.hemequity.com/raise-the-bar.

2. Introduction

Iron deficiency is the most prevalent micro-nutritional deficiency in the world.[1] Iron deficiency may present with or without anemia. Iron deficiency without anemia often goes unrecognized and is associated with symptoms that can negatively affect health related quality of life.[1-3]

Investigation of the underlying cause of iron deficiency is beyond the scope of this guideline. Iron overload is covered in a separate OAML guideline.

Readers are reminded that OAML Guidelines will not apply to every clinical situation, nor can they serve as a substitute for sound clinical judgment.

3. Causes of Iron Deficiency:

Table 1: Causes of Iron Deficiency

Increased Requirements	• Menstruating females • Pregnancy • Multiple pregnancies in rapid succession • Lactation • Growing infants and children • Erythropoietin treatment • Recent major surgery • Use of erythropoietin stimulating agents
Increased Loss	• GI bleeding • Menorrhagia • Persistent hematuria • Intravascular hemolytic anemias • Regular blood donors • Parasitic infections

Decreased Intake	• Vegetarian/vegan diet • Excess intake of dietary bran tannins, phytates, starch • Increased cow's milk • Decreased intake of iron rich foods • Low socioeconomic status
Decreased Absorption	• Upper GI pathology (e.g.: Celiac disease, inflammatory bowel disease, etc.) • Atrophic gastritis • H. pylori infection • Post-bariatric surgery • Gastrectomy • Chronic use of antacids

4. **Indications for Testing**

At-risk populations as defined in Table 1 with clinical signs and symptoms and patients with microcytic anemia should be considered for screening.[1,4]

It should be noted that although microcytic anemia is often due to iron deficiency, it can also be caused by hemoglobinopathies and anemia of chronic disease. The latter disorders are beyond the scope of this guideline but should be considered in the differential diagnosis and management. Failure to identify these other causes may result in unnecessary iron replacement.

5. Laboratory **Testing for Iron Deficiency**

Initial Testing
Routine laboratory test to be ordered in the investigation of iron deficiency are provided in Table 2.

Table 2: Laboratory tests for the investigation of iron deficiency:

Laboratory Test	When to Order
CBC	All patients
Reticulocyte count	All patients
Serum Ferritin	All patients
Serum Iron, Total Iron Binding Capacity (TIBC), and Transferrin Saturation	Patients with concomitant inflammation AND ferritin ≥ 30 µg/L (adult)* or ≥ 20 µg/L (pediatric)*

* For the purpose of diagnosing iron deficiency, the delineation of adult and pediatric patients in terms of age is somewhat ambiguous but, as a general guide, adult can be considered to be those ≥18 years of age and pediatric as those < 18 years of age.

Ferritin levels should be ordered with a complete blood count (CBC) in patients whose history suggests that they have risk factors for and/or symptoms of iron deficiency or iron deficiency anemia. Of note, a CBC alone is an inadequate screen for iron deficiency, as low hemoglobin and microcytosis (low MCV) are neither sensitive nor specific for iron deficiency.[1] In fact, most people with iron deficiency anemia have a normal MCV.[1]

Serum ferritin is the most sensitive and specific marker for iron deficiency in adults and in the pediatric patients. Ferritin is a positive acute phase reactant that rises with inflammation even in presence of iron deficiency. Examples of inflammatory states:

- Acute and chronic infections
- Heart failure
- Chronic kidney disease
- Autoimmune conditions (e.g., systemic lupus erythematous, rheumatoid arthritis, inflammatory bowel disease, vasculitis, psoriasis)
- Hematological and solid-organ malignancy
- Patients with elevated body mass index (BMI)
- Patient post-transplant

Adult patients who have ferritin ≥ 30 µg/L and pediatric patients who have ferritin ≥ 20 µg/L and concomitant inflammation (see examples above) should have full iron studies ordered (serum iron, TIBC, and transferrin saturation).[1] Iron studies should be ordered in the fasting state, as recent intake of iron-containing foods or supplements can affect serum iron and transferrin saturation. Ferritin concentration is not affected by recent food intake.

Additional Laboratory Tests for Consideration

C-reactive protein levels have been used to detect concomitant inflammation with levels >5 mg/L suggesting possible inflammation in patients with ferritin levels between 20 and 50 µg/L.[1]

Based on the behavior of the soluble transferrin receptor (sTfR) to hepcidin ratio, ferritin < 50 µg/L may be a sign of early iron deficiency.[1-2] Soluble transferrin receptor serum values may be used as an alternative to transferrin saturation to assess for iron deficiency in states of inflammation, especially in pediatric patients.[1] It is available to order as a separate laboratory test but may not be available at all community laboratories and is not an OHIP-insured test.

In the adult and pediatric populations, reticulocyte hemoglobin (CHr) is another measure that may identify early states of iron deficiency.[1] This is part of Reticulocyte testing but please note that this test is not available at all community laboratories. For more information regarding this test, please refer to the Raise the Bar website.[1]

6. Serum Ferritin Results Interpretation

Serum ferritin has a wide reference interval and historically has varied according to biological sex, however, a ferritin < 30 µg/L in adults and < 20 µg/L in children are appropriate clinical decision limits with an extensive supportive body of scientific literature.[1-2,5-6] These clinical thresholds are applicable across all community laboratories, despite the use of various Ferritin methods and some variability in results from laboratory to laboratory.[8]

Interpretation of ferritin levels and appropriate treatment are provided below and summarized in Table 3.

Table 3: Interpretation of Serum Ferritin Results

Serum Ferritin (µg/L)	Interpretation
<30 (adult) <20 (pediatric)	Consistent with iron deficiency

30-50 (adult) 20-50 (pediatric)	Probable iron deficiency (in the absence of concomitant inflammation)
51-100	Possible iron deficiency, if risk factors are present (in the absence of concomitant inflammation)
101- 300	Iron deficiency unlikely (in the absence of concomitant inflammation)

In adult patients, a ferritin result below 30 ug/L indicates iron deficiency. Ferritin is a positive acute phase reactant and may be elevated in the presence of inflammation. A ferritin result of ≥30 µg/L with a transferrin saturation result < 0.20 (20%) is consistent with iron deficiency or iron restriction (i.e. in presence of inflammation, access to iron stores is impaired leading to functional iron deficiency also known as iron restriction) and should be treated with iron replacement therapy.

In pediatric population, ferritin levels below 20 µg/L indicates iron deficiency. Similarly, to the adult population, in pediatric patients with concomitant inflammation, transferrin saturation < 0.20 (20%) is indicative of iron deficiency.[1]

A diagnosis of iron deficiency should trigger investigations to identify the underlying cause.

For treatment recommendations, please visit https://www.hemequity.com/raise-the-bar

7. Summary

Iron deficiency is the most prevalent micro-nutritional deficiency in the world.[1] Iron deficiency may present with or without anemia. Iron deficiency without anemia often goes unrecognized and is associated with symptoms that can negatively affect health related quality of life.[1-3]

Serum ferritin levels should be ordered with a complete blood count (CBC) in patients whose history suggests that they have risk factors for and symptoms of iron deficiency or iron deficiency anemia.

References

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