

## Iron Deficiency: Clinical Sequelae and Diagnosis

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There are three successive stages of iron deficiency in human beings: normal or even increased iron stores but iron-deficient erythropoiesis (functional iron deficiency); iron store depletion without anaemia; and iron-deficiency anaemia.

Iron deficiency is the most common nutritional deficiency. According to epidemiologic studies conducted in the United States, it is found in 2% of adult men aged up to 69 years and in 4% of adult men older than 69 years. Nine percent to 12% of Caucasian and 19% of African-American women present with iron deficiency. In a study concerning the prevalence of different causes of anaemia in western countries, iron deficiency is the main cause (29%), surpassing anaemia of chronic disease (27%) and anaemia secondary to acute bleeding (17.5%).

There are three causes of iron deficiency:

- Increased demand for iron, such as in that seen during infancy, adolescence, pregnancy, and lactation. Low socioeconomic status and poverty can exacerbate the iron deficiency occurring under these situations
- Iron loss. This cause is very frequent in young females because of menstruation and in the elderly with gastrointestinal tract pathology. Other causes of blood/iron loss include surgery, childbirth, haemoglobinuria, and haemoptysis. Finally, iron loss may be secondary to therapeutic or diagnostic procedures and/or blood donation
- Decreased iron intake results primarily from malnutrition and is by far the most common cause of iron deficiency in vegetarians. Less frequently, decreased iron absorption may be secondary to sprue, ulcero-hemorrhagic colitis, Crohn's disease, gastric or intestinal surgery, intestinal parasitosis (particularly *Helicobacter pylori* infection), and finally atrophic (autoimmune) gastritis

The main clinical manifestations of iron deficiency are the symptoms associated with anaemia, ie. fatigue, decreased tolerance for physical exercise, tachycardia, and pallor. Clinical manifestations of iron deficiency in rapidly proliferating tissues, such as skin, hair, and nails, include koilonychia, glossitis with burning tongue, dysphagia, and alopecia.

Diagnosis of iron deficiency is based on peripheral blood analysis (typical hypochromic, microcytic anaemia with poikilocytosis) and on levels of different iron parameters: serum iron, transferrin and ferritin levels. However, these parameters can be affected by inflammation and fasting, thus limiting their significance. Recently, soluble transferrin receptor (sTfR) levels and particularly sTfR/log ferritin have proven to be excellent tools for screening iron stores. sTfR parameters are especially useful in differentiating anaemia of chronic disease from iron deficiency anaemia and for the diagnosis of patients presenting with both conditions. Iron deficiency should also be differentiated from other causes of microcytosis, in particular thalassaemia.

In the past, bone marrow examination for stainable iron was regarded as the gold standard for diagnosing iron deficiency, but because of unacceptably high inter- and intra-observer variability in its evaluation, as well as the discomfort of the procedure, it is no longer recommended for routine evaluation of iron deficiency.

Patients with iron deficiency anaemia (IDA) and a high risk of underlying disease (eg, men of all ages and postmenopausal women) should be evaluated endoscopically for occult bleeding; video capsule endoscopy (VCE) should be considered in cases of suspected small-bowel malignancy.

Since there is insufficient evidence to support recommending routine screening for iron deficiency in asymptomatic persons, the US Preventive Services Task Force recommends such a screening only for pregnant women.

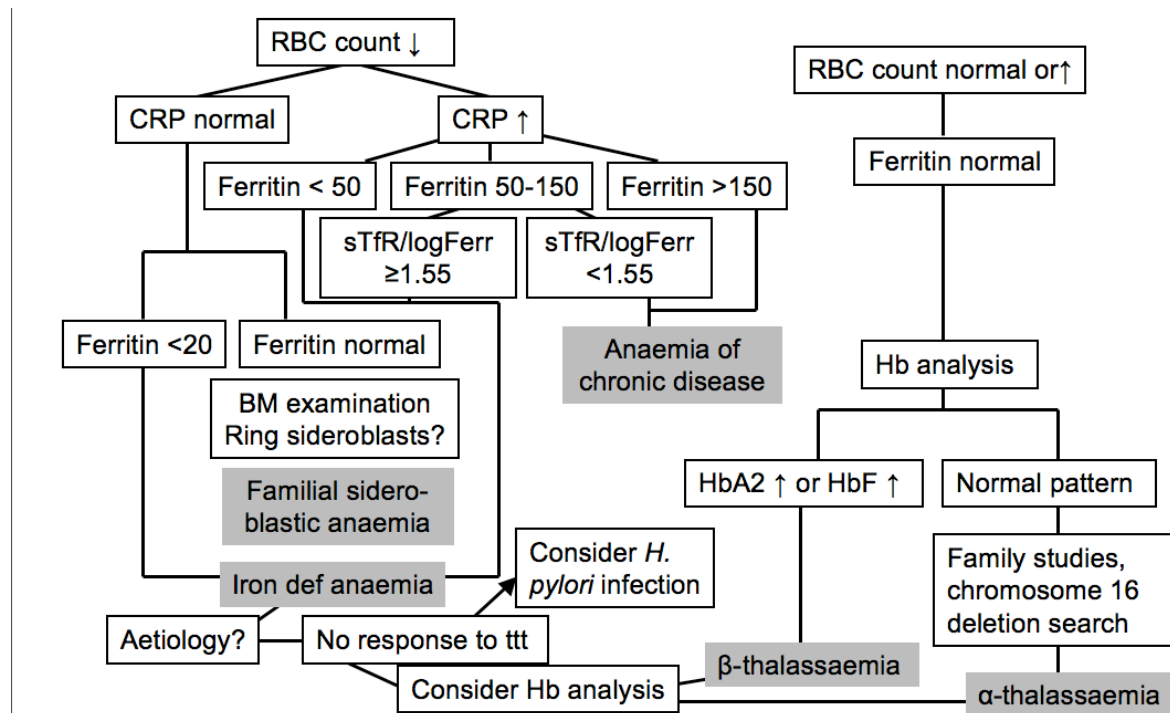
Diagnosis of functional iron deficiency is made in patients with:

- Normal or increased ferritin, and
- Laboratory signs of iron-deficient erythropoiesis: (serum iron <60 µg/dL, transferrin saturation <20%, hypochromic RBC >5%, reticulocyte Hb content (CHr) <29 pg, soluble transferrin receptor > 7 mg/L).

This situation is mainly seen in patients with anaemia of chronic kidney disease treated by erythropoietin and in patients with anaemia of chronic inflammation.

In recent years, *Helicobacter pylori* has been implicated in several studies as a cause of IDA refractory to oral iron treatment, responding favorably to *H. pylori* eradication. Other causes of refractory IDA are autoimmune atrophic gastritis or atrophic body gastritis, which has been associated with chronic idiopathic iron deficiency with no evidence of gastrointestinal blood loss. Thus, screening for *H. pylori* and atrophic gastritis is justified in (a) males and postmenopausal females with IDA and negative endoscopic and radiologic test results, and (b) fertile females and children/adolescents refractory to oral iron treatment.

We propose the following algorithm for investigation of microcytic anaemia:



In conclusion

- Iron deficiency causes not only anaemia but also extraerythroid symptoms
- Diagnosis of iron deficiency may be difficult in the presence of a concomitant inflammatory state

- Functional iron deficiency should be looked for whenever erythropoietin is used to correct anaemia
- IDA refractory to oral iron treatment is a new entity justifying a specific diagnostic work-up

### **Suggested Readings**

C Beaumont, P Beris, Y Beuzard, C Brugnara (editors). *Disorders of iron homeostasis, erythrocytes, erythropoiesis*. Genoa, Italy: Forum Service Editore, 2006.

Ferrara M, Coppola L, Coppola A, Capozzi L. Iron deficiency in childhood and adolescence: a retrospective review. *Hematology*. 2006;11:183-6.

Grosbois B, Decaux O, Cador B, Cazalets C, Jego P. Human iron deficiency. *Bull Acad Natl Med*. 2005;189:1649-63.

Killip S, Bennett JM, Chambers MD. Iron Deficiency Anemia. *Am Fam Phys*. 2007;75:671-8.

Trost LB, Bergfeld WF, Calogeras E. The diagnosis and treatment of iron deficiency and its potential relationship to hair loss. *J Am Acad Dermatol*. 2006;54:824-44.