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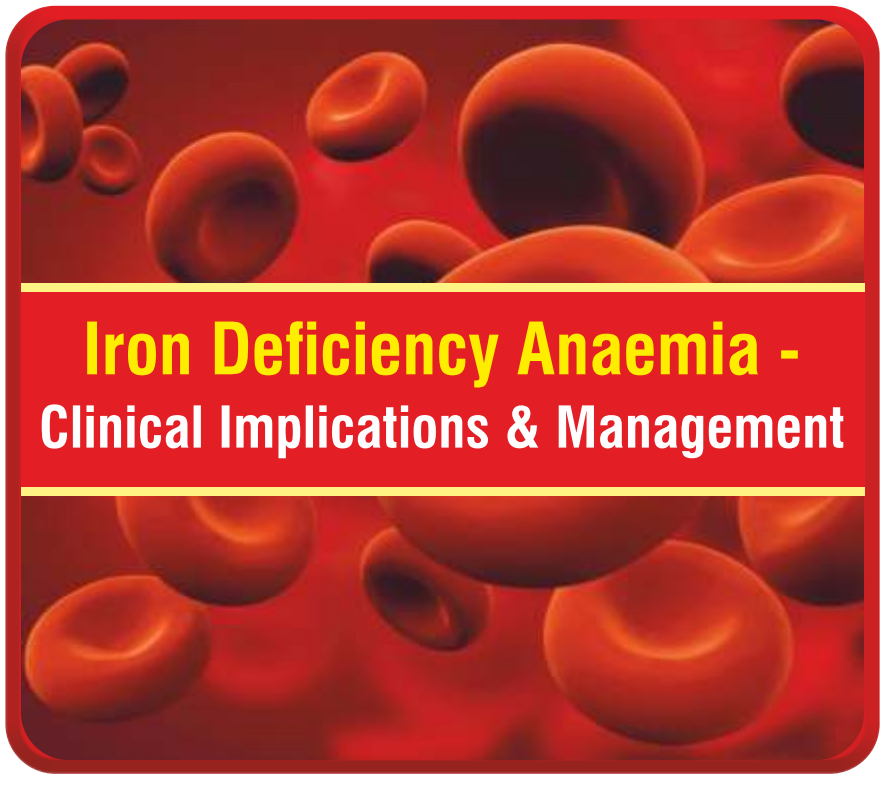

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Review:

Iron Deficiency Anaemia - Clinical implications & management

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Iron Deficiency Anaemia - Clinical implications & management

Introduction

Anaemia is a condition of reduced oxygen delivery by red blood cells (RBCs) to tissues. Either their number or oxygen-carrying capacity is insufficient to meet physiologic needs. The requirement of oxygen vary by age, sex, altitude, smoking, and pregnancy status. Iron deficiency is thought to be the most common cause of anaemia globally.[1] Although other conditions, such as folate, vitamin B12 and vitamin A deficiencies, chronic inflammation, parasitic infections, and inherited disorders can all cause anaemia. When severe, it is associated with fatigue, weakness, dizziness and drowsiness. Pregnant women and children are particularly more vulnerable. Iron-deficiency anemia (IDA) is the fourth leading cause of years lived with disability, especially in women. Thus, prophylaxis and management of ID is of paramount importance. Focus of IDA management is to find and address the underlying cause, especially in unexplained and/or recurrent cases, as well as to select the therapeutic option that safely meets the patient's needs.[2],[3]

Basic Iron physiology

Dietary iron

Dietary iron is present in two forms that is heme and nonheme iron.[4] Nonheme iron is plentiful in food of both animal and plant origins and is the main form of iron in plants. It is found in a wide variety of forms that includes soluble iron, iron in low-molecular-weight complexes, storage iron in ferritin, and iron in the catalytic centers of a wide range of proteins. Most non-heme iron is not tightly sequestered, as a result its bioavailability can be affected by a range of dietary constituents and luminal factors. The low pH of the stomach and proximal small intestine aids to keep iron in a soluble form, thereby making it available for absorption. Small organic acids such as citric acid and ascorbic acid also help to keep non-heme iron in a reduced and soluble form and can significantly increase its absorption.[4],[5] Some of the dietary constituents, especially plant-derived phytates, tannins, and polyphenols, can bind non-heme iron and hinder its absorption. On the contrary, heme iron is tightly sequestered within a protoporphyrin ring and is not accessible to the factors that influence non-heme iron. Therefore, heme iron tends to be absorbed more efficiently and its absorption is unlikely to be affected by dietary components. Most heme iron in the diet constitute myoglobin and hemoglobin, derived from animal sources.

Intestinal iron absorption

Iron is mainly absorbed in proximal parts of small intestine i.e., duodenum and first part of jejunum.[6] (Figure 1). Small quantity of iron is also absorbed by more distal parts of the gastrointestinal tract (GIT).

Iron cross both apical brush-border membrane and basolateral membrane of enterocytes to move from the lumen of intestine into the bloodstream. (Figure 1). Nonheme iron cross the brush-border membrane by binding with DMT1.[5] The prerequisite of DMT1 transporter is that it requires ferrous iron (Fe^{2+}) as a substrate. But most dietary iron is in the ferric (Fe^{3+}) form which need reduction to the ferrous form before it can be absorbed. Duodenal cytochrome B is one potential brush-border reductase,[7] that helps in conversion of Fe^{3+} to Fe^{2+} form. When sufficient amount of iron is absorbed, it becomes sequestered in the enterocytes into iron-storage protein ferritin. This amount is lost from the body once the enterocytes are sloughed off at the end of its life span. If the iron is required, it can be exported rapidly across the

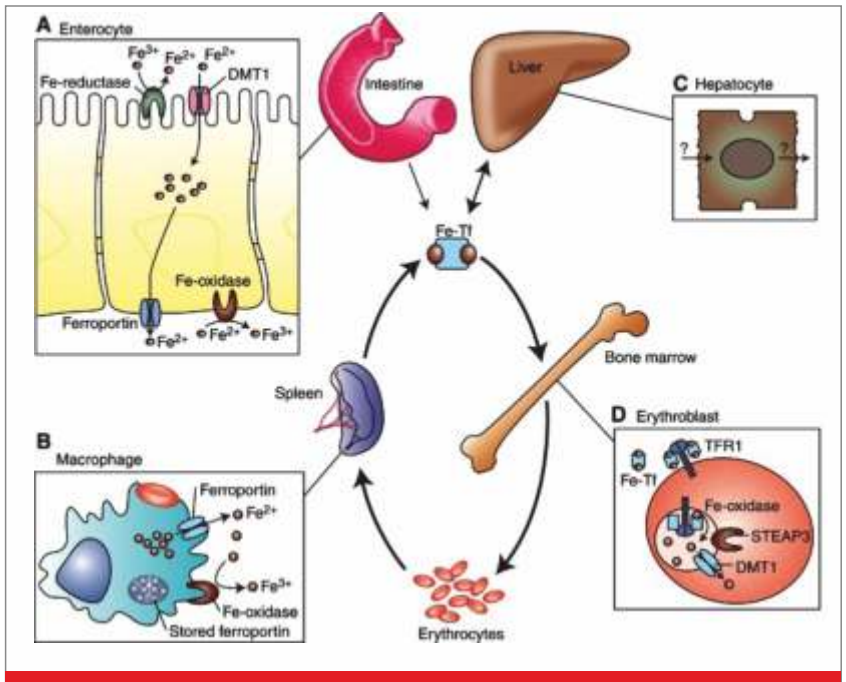

Figure 1: Body Iron Homeostasis

enterocyte basolateral membrane via ferroportin (FPN1).[8] The copper-dependent iron oxidase hephaestin, enhances efficiency of basolateral export of iron which helps in the conversion of newly transported Fe^{2+} to the Fe^{3+} form.[9]

Heme iron binds to the enterocyte brush border and is taken in by endocytosis. The action of heme oxygenases within the enterocyte, release iron from heme, which is subsequently exported from the cells via FPN1 (i.e., the same pathway as nonheme iron).[6]

Systemic iron transport and its delivery to tissues

Absorbed iron in the circulation (or iron that is released from storage sites) is bound to plasma transferrin which distributes it around the body to the sites of utilization[10] (Figure 1). Each transferrin molecule can bind ≤ 2 atoms of iron. Generally only about 30% of the iron-binding sites on the plasma transferrin pool are occupied at any one time [i.e., a transferrin saturation (TSAT) of 30%], thereby providing considerable buffering capacity against the appearance of potentially toxic non-transferrin-bound iron (NTBI). However, in iron-loading diseases, transferrin frequently becomes saturated, and the concentration of NTBI can be dangerously high.(11) TSAT can provide a useful index of iron supply to the bone marrow, and TSAT less than 16% indicates reduced production of new red blood cells (RBCs).(12) However, the mechanism involved is more complex than a simple restriction of iron supply for heme (and, hence, hemoglobin) production. It also involves the influence of low iron (among other signals) on various signaling pathways in developing erythroid cells.[13]

Diferric transferrin delivers iron to cells by binding to transferrin receptor (TfR) 1 on the plasma membrane[10] (Figure 2) by forming transferrin-TfR1 complex which are internalized via clathrin-mediated endocytosis. The endosome is acidified, and a combination of low pH, a conformation change in transferrin that is associated with its binding to its receptor, and a reduction of transferrin-bound Fe^{3+} via an enzyme of the 6-transmembrane epithelial antigen of the prostate family of reductases (6-transmembrane epithelial antigen of the prostate 3 in the case of immature erythroid cells) releases iron from transferrin.[14] This iron enters the cytoplasm transversing the endosomal membrane with the help of DMT1.[15]

Based on the iron requirements of the cell, its moves to sites of utilization such as the mitochondria and may be used for metabolic functions. If iron is not required immediately, it gets sequestered within the iron-storage protein ferritin for later use. The cell may also get rid of excess iron via export through FPN1. This export pathway acts as a safety valve if very large amounts of iron accumulated within the cell. In enterocytes, the efficiency of cellular iron export is enhanced by the iron oxidase hephaestin, whereas in most body cells, this role is played by the circulating hephaestin homolog ceruloplasmin.[16] Quantitatively, most iron is used by immature red blood cells in the bone marrow for hemoglobin production.

Apart from transferrin as source of cellular iron (Figure 2), NTBI can be taken up very efficiently by many other cell types. Zrt/Irt-like protein 14, an important NTBI transporter mediate the process.[16] There is some evidence that ferritin can deliver its iron to cells as

well.[17] At pathological state characterized by hemolysis, released heme and hemoglobin can bind to circulating hemopexin and haptoglobin, respectively. These formed complexes can be taken up by certain cell types,[18] providing important pathways for salvaging and reutilizing iron. The relative importance of different iron-uptake pathways varies between cell types. For example, immature erythroid cells are almost completely dependent on the TfR1-mediated endocytosis of diferric transferrin, but the liver utilizes a range of other pathways as well.[10]

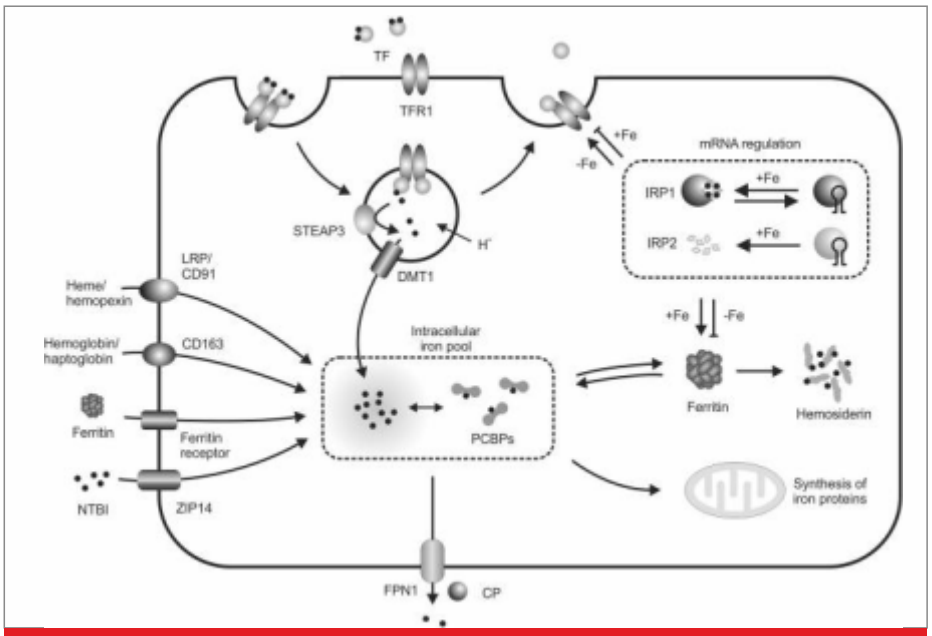

Figure 2: Cellular Iron homeostasis

Intracellular iron trafficking and storage

Free iron in solution is quite harmful hence, it is always maintained tightly sequestered by proteins. The cytoplasm contains iron-binding proteins, or chaperones, to move iron around the cell. The poly(rC)-binding proteins have been identified as intracellular iron chaperones (Figure 2) which delivers iron to ferritin and several enzymes.

Iron storage is an important component of cellular iron homeostasis. Generally, iron is sequestered in a nontoxic form which also acts as reservoir for future metabolic needs. Ferritin is the major intracellular iron-storage protein,[19] (Figure 2) with pores in the protein shell allowing the entry and exit of iron. A single ferritin molecule can hold ≤4500 atoms of iron, providing the cell with an huge capacity to store iron. When high concentrations of iron-laden ferritin accumulate within the cell, the ferritin molecules aggregate, which fuse with lysosomes. This process leads to degradation of ferritin, and the resulting mixture with Fe3+ cores and peptides is known as hemosiderin.[19] It is particularly prominent in the cells of patients with iron-loading diseases. Iron can be efficiently mobilized from these reservoirs, as and when required elsewhere in the body. Small quantities of ferritin are secreted from the cell, and the quantity that is secreted strongly correlates with the concentration of intracellular iron. This association makes serum ferritin concentrations a readily measured and accurate indicator of body iron stores.[19]

Systemic iron homeostasis

When a person needs more iron, it will be mobilized from body iron stores along with increased intestinal absorption. A small liver-derived peptide hepcidin regulates this process. However, if the body is iron replete, these processes will be downregulated. (Figure 1). Changes in body iron demand are communicated to the liver, which in turn, modulates the expression of hepcidin. Hepcidin is encoded by the hepcidin antimicrobial peptide gene, distributed via the circulation to its target tissues. It binds to the iron export protein FPN1 which acts as the hepcidin receptor. This complex is ubiquitinated, internalized, and degraded with the consequence that the capacity of iron to be released into the circulation is impeded. Therefore, when the body is iron replete, hepcidin concentrations are high, and the iron supply to the plasma is reduced; however, when iron demands are high, hepcidin concentrations are reduced, and more iron enters the circulation. Major site of iron storage are iron-exporting

cells; macrophages and intestinal enterocytes. Macrophages recycle heme-derived iron from senescent RBCs and hepatocytes. Intestinal enterocytes facilitate dietary intake of iron. However, most cells are able to export iron through FPN1 and, thus, are potential hepcidin targets.

The bone morphogenetic protein-SMAD regulatory pathway principally regulated by hepcidin. However inflammatory cytokines, hypoxia, and several other factors also can activate signaling pathways that lead to alterations in hepcidin transcription. Large iron stores and inflammation increase hepcidin expression, whereas it is reduced iron stores lead to hypoxia expression.

Organ - specific iron metabolism

The iron requirements of different organs is quite diverse.[20] Different cell types and tissues differ in their ability to take up and store various forms of iron. The erythroid marrow has the highest iron requirement for hemoglobin synthesis in new RBCs.[21] Tissues with a high proliferative capacity (e.g., the rapidly dividing cells of the intestinal crypts) also require relatively large amounts of iron, For example immature erythroid cells express abundant TfR1 on their plasma membrane.[22] Hence, when there is shortage of iron supply, the iron distribution to tissues becomes prioritized with erythropoiesis being particularly well protected. Similar condition is also observed during pregnancy when the iron supply to fetus is prioritized at expense of mother.[23]

Pathophysiology of iron deficiency

Normally body contains 3 to 5 g iron. Alteration in this range can lead into either ID or iron overload and their pathological consequences.[11],[1] An insufficient iron supply may impair the synthesis of essential iron-containing proteins, required for normal cellular physiology, consequently resulting in a range of adverse conditions. On the other hand, excess iron may catalyze reactions that produce reactive oxygen species.[11] The consequent oxidative damage to cells and tissues can lead to tissue fibrosis and organ dysfunction in long term. The absence of anaemia does not exclude ID, because an individual has to lose most of iron stores before the hemoglobin (Hb) can fall to values defined for anaemia. As a matter of fact, WHO declares that "mild anaemia" is a misnomer, as ID could be well advanced and causes clinical symptoms before Hb reaches the threshold for anaemia. Hence ID is the disease, and anaemia is just one of its consequences.[17]

Iron deficiency anaemia

Iron deficiency is the most common cause of anaemia. World Health Organization (WHO) has defined anaemia as Hb < 12 g/dL for women and Hb < 13 g/dL for men. The primary causes of IDA can be broadly classified as increased demands, reduced absorption and/or increased loss of iron.[24],[25] Insufficient dietary intake is the main cause of ID,[1] and low iron bioavailability of plant-based diet enhances susceptibility to ID.

Pathophysiology

Iron is essential for hemoglobin synthesis. Iron-deficiency anaemia could arise secondary to depletion of iron stores as a result of blood loss, decreased intake, impaired absorption, or increased demand (Table 1). Iron deficiency will lead to microcytic hypochromic anemia on the peripheral blood smear. Adults > 50 years of age with iron-deficiency anaemia and gastrointestinal bleeding need to be evaluated for malignancy. However, gastrointestinal diagnostic evaluation fails to establish a cause in one-third of assessed patients. Because iron

is the most common single-nutrient deficiency, the American Academy of Pediatrics recommends supplementation. When to begin supplementation and the needed dosage depends on the age and diet of the child.

Table 1: Main causes of iron deficiency anaemia

Increased iron losses	Limited external supply or absorption	Increased demands:
• Bleeding trauma • Gastrointestinal bleeding (peptic ulceration, neoplasia, inflammatory bowel disease, vascular malformations, medications [anti-inflammatory, anti-platelet or anticoagulant agents]) Genitourinary bleeding Menses and multi-parity Multiple diagnostic phlebotomies (medical "vampirism") Blood donation	• Poor intake • Inappropriate diet with deficit in bioavailable iron and/or ascorbic acid (including excess of dietary fiber, phenolic compounds from tea or coffee, and soya products) • Malabsorption (autoimmune atrophic gastritis, gastric resection, bariatric surgery, inflammatory bowel disease, celiac disease, non-celiac gluten sensitivity, Helicobater pylori infection) • Medications (AntiH2, PPI, antacids, etc.) • Increased hepcidin levels (e.g., IRIDA or ACI) • Molecular defects in iron transport	• Body growth (infancy and childhood) • Pregnancy and lactation • Recovery from blood loss • Treatment with erythropoiesis

ACI, anaemia of chronic inflammation; AntiH2, histamine H2 receptor antagonists; DMT1, divalent metal transporter 1; IRIDA, iron-refractory iron deficiency anaemia; PPI, proton pump inhibitors

Prevalence of iron deficiency across pathologies is depicted in figure 3. The anaemia of chronic disease or of inflammation is the second most common form of anaemia, next to that caused by ID.[26] In response to inflammatory situations such as infection, cancer, and various chronic inflammatory states, the plasma iron concentration decreases. If this condition persists, the iron supply to the erythroid marrow can be compromised, and anaemia may result. At the molecular level, much of the reduction in plasma iron that accompanies anaemia of chronic disease can be explained by the stimulation of hepcidin production by proinflammatory cytokines. Higher hepcidin concentrations reduce cell-surface FPN1 and result in iron sequestration within cells. However, FPN1 expression may also be reduced independent of hepcidin during inflammation.

History and Physical

Generally, most IDA patients are asymptomatic and first diagnosed through a blood test. Pallor is the most common and significant clinical sign, but it is not usually visible until hemoglobin falls to 7 g/dL to 8 g/dL. Table 2 enlist the normal values of Hb (haemoglobin) for each age group.

Some diagnostic clues can be achieved by patient's medical history (including signs and symptoms of ID and co-morbidities). In severe anemia a thorough history may reveal fatigue, decreased ability to work, shortness of breath, or worsening congestive heart failure. An anemic child may present with cognitive impairment and developmental delay. However, generally, clinicians will not relate chronic fatigue to ID. As a result, ID without anemia is almost invariably a casual laboratory finding.[27]

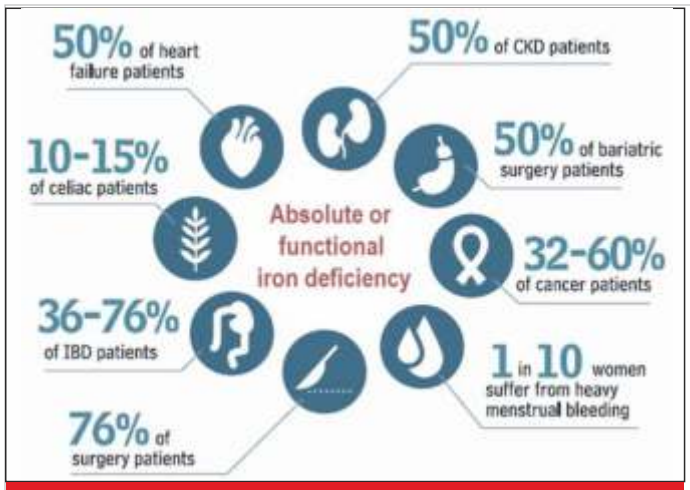

Figure 3: Prevalence of iron deficiency in different disease conditions

History regarding diet, any bleeding from menorrhagia or gastrointestinal sources should be elicited. The physical exam may reveal pale skin and conjunctiva, resting tachycardia, congestive heart failure, and guaiac-positive stool.

The stool guaiac test or guaiac fecal occult blood test (gFOBT) is one of several methods that detects the presence of fecal occult blood . The test involves placing a faecal sample on guaiac paper and applying hydrogen peroxide which, in the presence of blood, yields a blue reaction product within seconds.

Laboratory work-up

Diagnosis of anaemia is possible with sign-symptoms and basic physical examination. Laboratory evaluation is important for identifying anaemia. The flow chart (Figure 5) below divide anaemia as per MCV values. IDA reduces mean corpuscular hemoglobin (MCH; normal range 28–35 pg). So, even with normal Hb level range, ID will increase red cell distribution width (RDW, normal range 11-15)[25],[28] Serum ferritin concentration < 30 ng/mL is most accurate definition of ID. [29] (Figure 4)

Serum ferritin indicate the total body iron stores. Serum levels of ferritin, iron, and transferrin saturation will be reduced in ID. The total iron-binding capacity will be increased. A serum ferritin < 100 ng/mL with a transferrin saturation (TSAT) < 20% is also suggestive of ID, especially in the presence of inflammation (Figure 4) whereas, serum ferritin > 100 ng/mL with a TSAT < 20% usually suggests iron sequestration (also referred to as functional iron deficiency, FID). Erythropoiesis-stimulating agents (ESA) may also result in FID.[25],[28]

*Low reticulocyte Hb content (<28pg), increased hypochromic red cells (>5%) or high soluble transferrin receptor to log ferritin ratio (>2) could identify a component of an absolute iron deficiency in the presence of an inflammation- induced high ferritin level (Figure 4)

Microscopic examination will reveal microcytosis, hypochromia, and anisocytosis, as reflected by a red cell distribution width higher than the reference range. Gastrointestinal source of bleeding can be identified by stool examination for occult blood.

Mentzer index or simple mean corpuscular hemoglobin/RBC index, helps to differentiate between the two causes of microcytic/hypochromic anemia i.e., iron deficiency and thalassemia minor. An index > 15 suggests iron deficiency, while an index less than 11

Table 2: WHO's Hemoglobin thresholds used to define anemia (1 g/dL = 0.6206 mmol/L)

Age or gender group	Hb threshold (g/dl)	Hb threshold (mmol/l)
Children (0.5 - 5.0 yrs)	11.0	6.8
Children (5–12 yrs)	11.5	7.1
Teens (12–15 yrs)	12.0	7.4
Women, non-pregnant (>15 yrs)	12.0	7.4
Women, pregnant	11.0	6.8
Men (>15 yrs)	13.0	8.1

suggests thalassemia minor. The definitive test to rule out thalassemia minor is hemoglobin electrophoresis.

Severe or non-responding cases may require an iron profile. Low ferritin is a reliable marker of iron deficiency. Being an acute phase reactant, ferritin levels are high in inflammatory conditions such as malignancies, infection, and collagen disease. In these cases, alternate parameters are used. These are low reticulocyte Hb content, increased hypochromic red cells (>5%) or a high soluble transferrin receptor to log ferritin ratio (>2).[25],[28] The bone marrow aspiration or biopsy followed by iron staining is the ultimate test. However, the cost and invasiveness of this test make it less feasible; and is rarely performed.

Treatment of IDA

The treatment of underlying cause, such as gastrointestinal bleeding is crucial to control the loss. The deficiency can be replenished by increasing the consumption of iron rich diet or by taking supplements.[1] Commonly used iron supplements; ferrous sulfate, ferrous gluconate, peptonized iron, and ferrous fumarate[30] are effective. Low gastric pH facilitates iron absorption, so supplements are prescribed on empty stomach. A rapid response, with increase in hemoglobin level is often seen by 14th day. But continuous treatment over at least three months replenish tissue iron stores. On achieving normal hemoglobin levels too, iron supplementation should proceed for at least a month. However iron at high doses, can lead to significant gastrointestinal side effects.[31]

The adverse effects of oral iron include constipation, nausea, decreased appetite, and diarrhea. Parenteral iron supplements have better bioavailability,[30] and less intolerance than

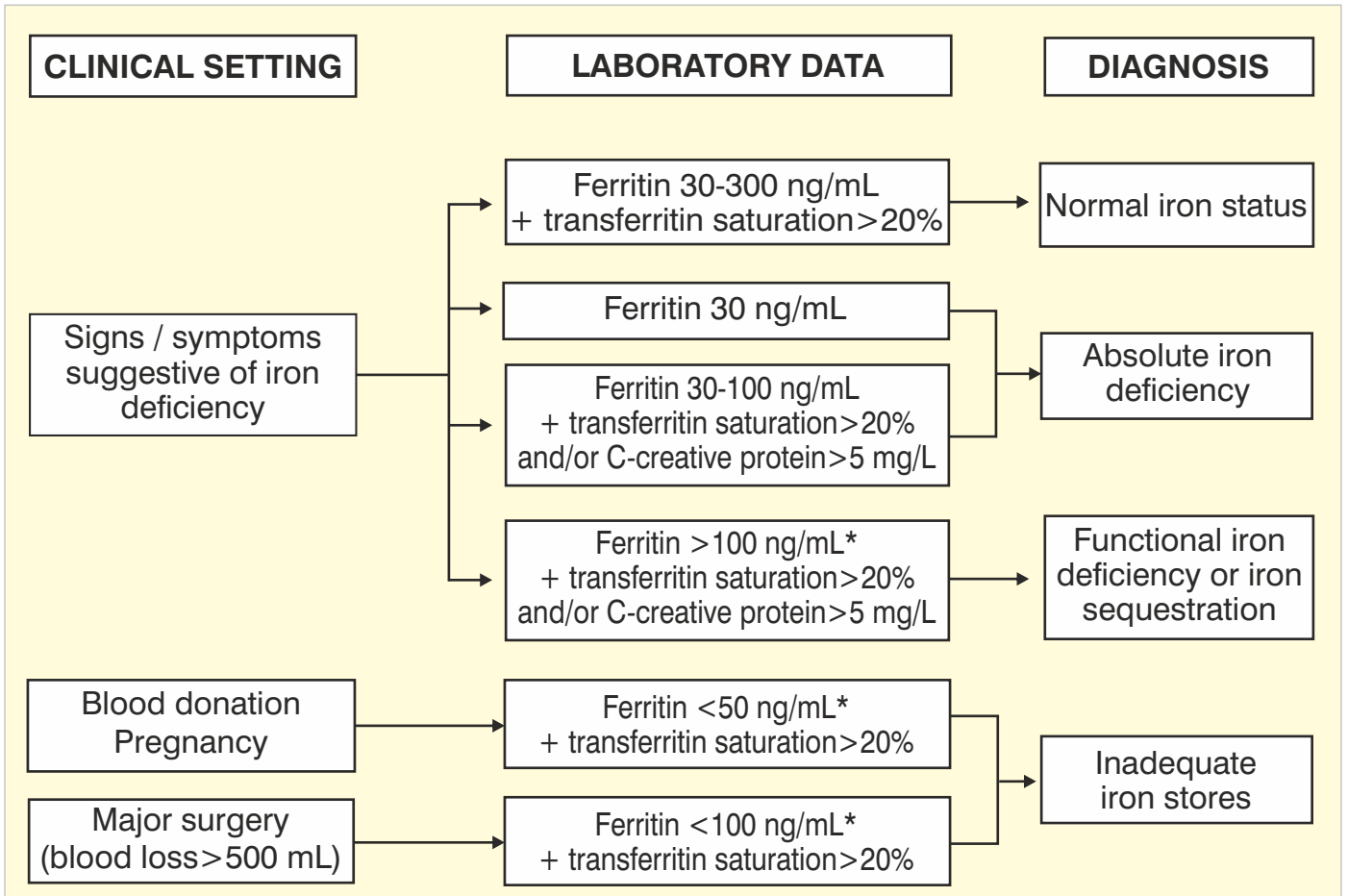

Figure 4: Laboratory assessment of iron status

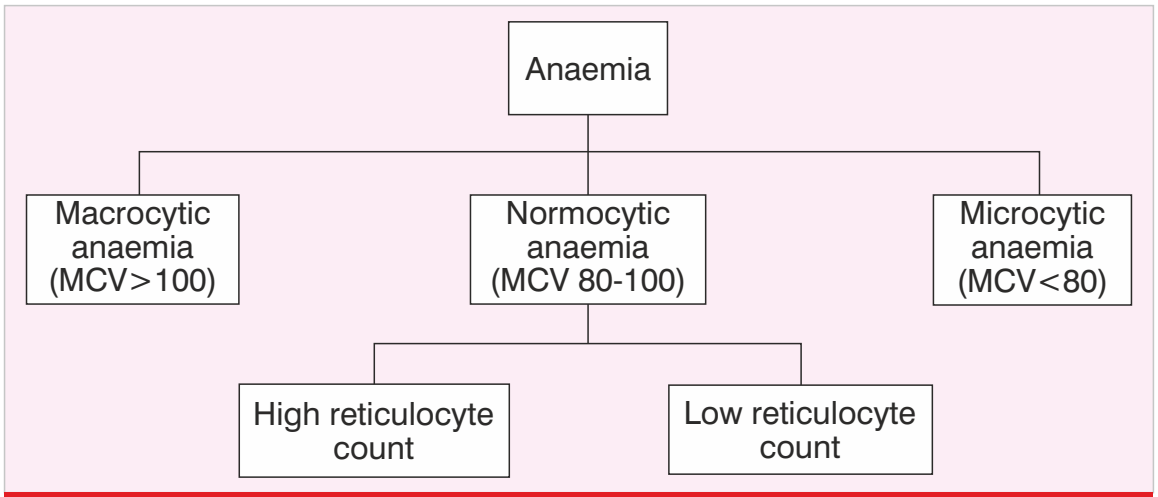

Figure 5: Classification based on MCV values

oral iron. Hence in cases of severe ID, malabsorption such as celiac disease, post-gastrectomy or achlorhydria, or if losses are too high for oral therapy; an intravenous iron infusion may be warranted to deliver a large amount of iron quickly. Although intravenous iron is more reliably and quickly distributed to the reticuloendothelial system than oral iron, it does not provide for a more rapid increase in hemoglobin levels. But its adverse effect include most commonly nausea, and rarely anaphylaxis. Extravasation of iron solutions into the subcutaneous tissue causes brownish stains that can be permanent and aesthetically unpleasant for the patient. Dietary counseling is usually necessary for management. The decision on oral and intravenous route Vs blood transfusion, depend on the patient's Hb levels, tolerance and co-morbidity. Whether it is a new onset, recurrent, explained or unexplained should also be considered for choosing among the different ID treatment options. Along with supplementation, teenage girls who are experiencing excessive menstrual blood loss may benefit from hormonal therapy.[23,32]

Oral iron supplementation

Oral supplements in the form of ferrous or ferric salts, are generally the first line of treatment for uncomplicated IDA. They have reasonable bioavailability, but are easy to administer at relatively low cost.[33] Dose for treating IDA is 100–200 mg elemental iron, to be taken 1-3 times a day. However, the bioavailability is 10% to 15% for ferrous iron preparations (sulfate, gluconate, fumarate, etc.), and it is even lower for ferric iron salts or ferric iron complexes (amino acids, polysaccharide, ovo-albumin, etc.). The side effects can be minimized by giving iron in divided dose (40–60 mg thrice a day) in a day rather than as a single dose. This is also associated lower hepcidin secretion, resulting in better treatment compliance and enhanced fractional absorption.[34] Though not proven by clinical trial, this emerges as a new paradigm for oral iron supplementation in ID treatment.[28] Concomitant administration of other drugs, such as proton pump inhibitors or antacids, or meals, and the presence of an inflammatory status may prolong the duration of treatment or even render it ineffective.[35] Moreover, up to 50% of patients on oral iron (depending on the iron formulation) report gastrointestinal side effects due to the direct toxicity of ionic iron, which may lead to reduced tolerance and adherence.[36]

Peptonized iron formulation is a hematinic specially formulated to treat iron deficiency anemia. In this formulation, iron is administered along with proteins in the form of Peptone. It has been realized that although iron content of a hematinic formulation is important, of greater nutritional significance is the bioavailability of iron.[37] Two factors that increase the absorption of iron are ascorbic acid and animal proteins.[37],[38] Between the two, it was noticed that the effect of proteins on iron absorption was much greater than that of ascorbic acid.[38]

It has been reported that iron absorption is 2 to 4 times higher in the presence of proteins.[39] In a review examining the effect of dietary proteins on iron bioavailability, the effects of protein on iron absorption from five different studies were analyzed. It was noticed that the administration of protein increased the bioavailability of dietary iron by 1.7 to 4.4 times and that the average increase in absorption of iron was by 2.6 times.[40]

The exact mechanism for this increased in bioavailability is not known. One of the mechanisms may be an increase in the secretion of gastric acid.[37] However, it is realized that although most proteins increase the secretion of gastric acid, not all of them increase iron absorption; rather proteins present in eggs & soya have been reported to significantly reduce the absorption of iron.[39],[40] Thus mechanisms other than increased acid secretion seem to be responsible for the increased iron absorption that occurs in the presence of animal protein.(37) One recent study has reported an increase in the expression of divalent metal transporter-1 (DMT-1) by 3.2 times and duodenal cytochrome b (Dcytb) by 1.8 times when iron was administered along with proteins.[41] DMT-1 is the channel through which iron is taken up by the intestinal mucosal cells while Dcytb is a reductase responsible for reducing the Ferric form of iron into the ferrous form. Thus, the increased expression of DMT-1 and Dcytb may be partly responsible for the increased bioavailability of iron in the presence of proteins.

Peptonized iron is the source of iron which is a reversible complex of iron with peptone. Although peptonised iron is freely soluble in water, iron stays bound to protein and does not ionize in water. As a result, unlike conventional iron salts, Hepatoglobine causes relatively less staining of teeth or tongue. Moreover, as iron is not free, it is unlikely there is interaction with substances present in food, like phytates, phosphates & tannates, which bind to iron and reduce its absorption.[42]

Intravenous iron supplementation

With intolerance or no response to oral iron salt, iron therapy should be switched to intravenous (IV) route.[33] Different commercially available IV iron formulations for clinical use are ferric gluconate (FG), iron sucrose (IS), low molecular weight iron dextran (LMWID), ferric carboxymaltose (FCM), ferumoxytol (FXT), or iron isomaltoside 1000 (ISM). Irrespective of their dose-dependent efficacy for correcting ID, "newer" IV iron formulations, such as FCM or ISM, which allow for a short-time (15–60 min) infusion of high iron doses (1000 mg or more), are preferred by both physicians and patients.[35]

Intravenous iron formulations are more expensive than oral iron and require venous access (side effects at the injection site may occur) and infusion monitoring (there is still a risk of infusion and hypersensitivity reactions). The European Medicines Agency recommended that "IV iron products should be administered only when staff is trained to evaluate and manage anaphylactic reactions, and resuscitation facilities are immediately available". Except for the chronic kidney disease population, long-term safety data of IV iron are still inadequate.[35]

Red blood cell (RBC) transfusion

In case of severe IDA with alarming symptoms (e.g., hemodynamic instability) and/or risk criteria (e.g., coronary heart disease), patient should be treated with red blood cell transfusion, using the minimal amount necessary to achieve clinical stability. Adhering to patient-adapted restrictive transfusion criteria and transfusing one unit at the time, with post-transfusion reassessment, is strongly recommended by most guidelines. Red blood cell transfusion leads to a rapid, albeit transient, rise in Hb, thus increasing oxygen-carrying capacity. However, severe IDA will recur unless the underlying cause is identified and treated. Additional iron supplementation should be administered once the hemodynamic stability has been achieved by red blood cell transfusion.[3]

Iron deficiency anaemia in pregnancy

Pregnancy and puerperium

Iron deficiency during pregnancy and the puerperium is responsible for increased maternal and fetal morbidity and mortality. Though influenced by severity of deficiency and comorbidity, it is among the commonest risk factors in obstetric and perinatal medicine (Table 3). As per WHO, the estimated worldwide prevalence of anaemia in pregnancy is 30% to 50%, depending on geographic area. Postpartum anaemia continues to be among the commonest causes of death in women who have just given birth in developing countries. In Europe, approximately 10% of women in the puerperium have moderate-to-severe anemia, and adequate treatment of which without recourse to allogeneic blood is a current problem.[43],[44]

Symptoms of iron deficiency

Fatigue, headache, hair loss, poor concentration, pica, restless legs syndrome, and reduced physical performance, are in general indications for intervention. In severe IDA symptoms can include decreased physical and work capacity, increased cardiovascular stress (tachycardia, hypotension), reduced thermoregulation, and increased susceptibility to infection. Moreover, a consequence of the ID in various enzyme systems, such as oxidoreductases, mono-oxidases, dioxygenases, and especially decreased mitochondrial activity in the body cells, may lead to symptoms independent of anaemia.

Clinical studies have shown a positive influence of iron administration on symptoms independent of anaemia.[45], [46],[47] The effect of iron does not correlate directly with the amount of iron administered or the ferritin level.[47] Certain symptoms, such as fatigue, may only suggest but not prove iron deficiency. People without iron deficiency may have the same degree of fatigue as people with iron deficiency. The specificity of the symptom "chronic fatigue" for iron deficiency (ferritin < 15 g/L) is only 20%. Thus, if ID is suspected as the cause it should always be confirmed with laboratory blood test.

Consequences of iron deficiency in pregnancy

Depending on the severity of iron-deficiency anaemia, mortality is increased because of cardiovascular insufficiency, a higher risk of hemorrhagic shock, higher infection rates in the puerperium, and poorer wound healing. Post pregnancy, tolerance to peripartum blood loss is greatly reduced.[46],[48] Maternal morbidity is related to factors such as socio-economic status, availability of medical care, and nutritional state. A problem interpreting available published evidence is that maternal and fetal outcomes are related to the severity of the anemia but not to the duration and time of first appearance of anemia or the duration and time of onset of iron deficiency. Taking this limitation into account, some authors postulate a correlation between maternal mortality and degree of anemia (Table 3).

*Reduced capacity to breast feed and/or reduced quantities of breast milk

There are currently no studies on the relationship between iron-deficiency anemia before pregnancy and subsequent outcomes. No prospective studies in large cohorts that show the effect of early intervention and treatment of anemia on maternal, fetal, and neonatal outcome are available. Even the critical hemoglobin level is in relation to maternal mortality is unclear (Table 4).[49],[50]

*The influence of external factors, such as iron deficiency on fetal gene expression (epigenetics)

Diagnostic principles

During pregnancy the diagnosis and consequent management are based on the differentiation between the relative or physiologic anemia of pregnancy due to increased

Table 3: Risk groups for the development of iron deficiency and iron-deficiency anaemia

During pregnancy	Postpartum
After first trimester	Iron deficiency and iron-deficiency anemia during pregnancy
Iron deficiency in prior pregnancy	High blood loss at delivery
Multiparity	Poor socio-economic status
Short recovery between pregnancies	Poor nutritional status
Multipara	
Poor socio-economic status	
Poor nutritional status	

plasma volume and "true anemia" with its different pathophysiological causes. When defining the cutoff value for anemia in pregnancy, the degree of changes in plasma volume at varying gestational age must be taken into account. Accordingly, hemoglobin concentrations <11.0 g/dL in the first and third trimester and <10.5 g/dL in the second indicate possible anemia, which requires further investigation.[51] The cause of anemia in pregnancy is multifactorial and just to diagnosis based on the hemoglobin concentration is not enough so the causes should always be investigated.

Different causative factors, which are accompanied by reduced hemoglobin synthesis, increased hemoglobin breakdown, or hemoglobin loss, need to be considered in the differential diagnosis. A common example is the combination of decreased hemoglobin synthesis and increased cell death seen in thalassemia syndromes, a result of which may complicate diagnosis and treatment. The most important differential diagnoses include iron-deficiency anemia and its precursors (to which often too little attention is paid), hemoglobinopathies (thalassemias, sickle cell anemia), anemia of infection, and anemia of chronic kidney disease.[44],[52]

A detailed history and clinical examination of the pregnant woman is critical for correct diagnosis. The current gold standard for detecting iron deficiency is still the serum ferritin level. However, because of its acute phase reactivity, it may be spuriously elevated, missing the diagnosis. If the serum ferritin is not below the lower limit of normal, the percentage of transferrin saturation remains the most reliable indicator of iron need. The reticulocyte hemoglobin content, when routinely available, promises to facilitate the diagnosis of iron deficiency even further.[53]

Table 4: Maternal consequences of anaemia

- Mortality with high blood loss
- Cardiovascular strain
- Reduced physical and mental performance
- Reduced peripartum blood reserves
- Increased risk of peripartum blood transfusion
- Insufficient milk syndrome* in postpartum anemia

Serum ferritin level has the highest sensitivity and specificity for detecting ID. Ferritin levels of <20 ng/mL are diagnostic of ID, regardless of the hemoglobin concentration. Ferritin levels between 20 and 50 ng/mL are regarded as a gray area. If ferritin levels are within the normal range (>50 ng/mL), IDA can be virtually ruled out,

Table 5: Foetal risks linked to maternal anaemia and iron deficiency

- Intrauterine growth retardation
- Prematurity
- Death in utero
- Infection
- Fetal programming (fetoplacental miss ratio)*

unless a concomitant active infection or other inflammatory process is present. A false-normal result for Serum ferritin is possible during inflammatory reactions and even postoperatively, still it correctly represents the iron stores 6 weeks after surgery or childbirth. On suspicion of concomitant presence of iron deficiency and anemia, the presence of infection or inflammation must always be excluded by using the sedimentation rate or CRP. In special cases, iron investigations may be supplemented by various parameters, such as serum transferrin receptors, ferritin index, zinc protoporphyrin, and percentage of hypochromic red cells.[53]

Serum iron, transferrin, transferrin saturation

Usually, assay of serum iron and transferrin levels (total iron binding capacity) have no added benefit during investigation of iron deficiency. Even in pregnancy, the serum iron levels are subject to diurnal, intra-individual and inter-individual variations. So, actual iron status is determined by percentage of transferrin saturation.

If the ferritin levels are within the normal range, but the transferrin saturation is less than 15%, it indicates latent iron deficiency since iron is being released in higher quantities from circulating transferrin to maintain erythropoiesis. But fluctuations in serum iron levels also affect calculation of transferrin saturation and thus may lead to incorrect interpretations.[54] Therefore sample drawn after an overnight fast are ideal as dietary iron may influence the percent transferrin saturation.

Transferrin receptors

The soluble transferrin receptor (sTfR) is a sensitive and specific indicator of change in iron kinetics. It increases in iron deficiency or if there is an increased cellular iron requirement. As transferrin receptors are probably not affected by infections, they represent a useful addition to ferritin assays. During trial, low sTfR levels in early pregnancy appear to be associated with inhibited erythropoiesis in the first trimester. The increase in sTfR during pregnancy is attributed to an increasing stimulation of erythropoiesis and an increasing iron requirement by iron-dependent cell proliferation. Whether inhibited erythropoiesis at early pregnancy negatively influences detection of concomitant iron deficiency through measurement of sTfR, is not known. There is nothing to suggest that the sTfR concentration is influenced by inflammatory reactions. Thus, this parameter would also be useful for the investigation of unclear situations in pregnancy (normal ferritin in the presence of an elevated CRP) and in the early puerperal phase. In a study, after labor sTfR concentrations were not influenced by the inflammatory reaction at birth, in contrast to ferritin levels.[52] (Table 6)

Prevention and treatment of iron deficiency in non-pregnant women

Availability of iron from food depends on its iron content, amount ingested, absorption of iron in the intestine and subsequent bioavailability. Adequate dietary intake can compensate for normal iron losses though compensating for higher iron losses through diet is unrealistic with existing eating habits and quantities. Even meat has high iron content up to 2 mg/100 mg, but intestinal absorption is only 1% to 20%, depending on whether the food is of animal or vegetable origin. A daily requirement of 2 mg iron per day is covered by 300 g meat/fish. For vegetable sources, lacking heme iron, requirements are higher (1000 g soya beans or 5000 g spinach).[48] Since general population lack knowledge and need guidance and motivation.

Oral (tablets or drops/syrup) iron preparations are available as Fe II salts or Fe III complexes, whose absorption is between 1% and 8% depending on composition. Thus 80-mg tablet/d corresponds to just under 8 mg iron absorption/d. Though even daily doses of 20 mg Fe II salts result in a significant improvement in symptoms. With increasing dose (>100 mg/d), the

gastrointestinal side effects of oral iron increase because of the toxic oxidative effect of iron in cells.[36] It leads to reduced adherence and irrespective of the preparation, almost 20% of women stop oral iron therapy. In general, iron (III) complexes show better gastrointestinal tolerability but are absorbed to a lesser extent.[55]

If ID is not corrected by oral preparations, intravenous iron (iron sucrose, ferric carboxymaltose [FCM], iron dextran, iron gluconate) is recommended. Iron sucrose is most commonly used formulation but FCM and low-molecular-weight iron dextran (LMW ID) too are being studied. Due to higher rates of gastrointestinal disorders (16 vs 3) with oral iron, during late-stage pregnancy, intravenous iron is the appropriate first-line option for rapid and effective anemia correction. It also has additional benefits for vitality and social functioning.[56] On comparison, available listed formulations, including LMW ID (1000 mg) and FCM, have equivalent safety and efficacy.[57] However, iron sucrose and ferric gluconate need multiple visits to accomplish what a single infusion of LMW ID or FCM can do in 15-60 minutes with improved convenience and cost to patients, physicians, and ancillary personnel.

Severe allergic reactions with any of the formulations are rare. The rate of adverse reactions is approximately 1% to 5%, which include dizziness, flushing, pressure in the chest or back, limb pain, and flu-like symptoms. Extravasation must be avoided during parenteral iron administration because intravenous iron causes persistent skin discoloration.[58]

Sustained iron therapy

Identification and correction of iron loss should be done simultaneously with intravenous iron therapy. Vegetarians who menstruate and consume little iron in their diet are not able to replenish or maintain replenished stores. Women with periodically high iron losses (menstruation, blood donors) or consumption (competitive sportswomen because of increased loss in extreme exercise, pregnant women) are similarly unable to maintain stores.

Table 6: Laboratory parameters in iron deficiency and anaemia

	Hemoglobin	MCV	S-Ferritin	TSAT	sTfR
ID	N	N ↓	↓	N	N
IDA	↓	N-↓	↓	↓	↑
ACD	↓	N-↓	N-↑	N-↓	N

ACD, anaemia of chronic disease or inflammatory states; ID, iron deficiency; IDA, iron-deficiency anaemia; MCV, mean cell volume
N, normal; S-ferritin, serum ferritin; TSAT, transferrin saturation; , high; , low

Prevention and treatment of iron deficiency anaemia in pregnancy

The cause and severity of anemia along with maternal and fetal risk factors direct the course of treatment. The time period available for correction of anemia before childbirth influences the choice of intervention. Parenteral iron formulations are safe and well-tolerated. Preterm labor, peripartum bleeding, delay in growth and development of intrauterine fetus, cognitive and behavioral abnormalities of born child can be prevented by proactive intervention.[59] The administration of allogeneic blood should be a last resort in pregnant women and those in the puerperium. Recombinant erythropoietin may be necessary in extreme cases.[60]

Prevention

Body's iron status can improve with: reduce losses, limit consumption, and increase intake. Major blood loss should be avoided at puerperium.The interval before subsequent pregnancy may be used for replenishment. In pregnancy, however, the only option is pharmacologic supplementation.

Pharmacological supplementation

Preventive iron administration is recommended and practiced in industrialized countries. Regular administration of iron preparations without actual knowledge of iron stores, continues to be a subject of debate. Though iron deficiency has worldwide prevalence, the consequences of anemia Vs possible harmful effects of nonselective iron administration on the mother are debated. Latest Cochrane Database give no scientific or medical justification for prophylactic iron administration in pregnancy in countries with adequate nutritional resources because epidemiological data do not show any positive effect on the course of pregnancy and/or maternal and fetal outcome.[61]

Though in terms of hematological data (ferritin levels, hemoglobin), randomized, placebo-controlled trials do show a positive effect. Women with low iron stores at the start of pregnancy develop anemia less often if they receive iron supplementation. Thus iron supplementation is indeed justified in countries with a high prevalence of iron-deficiency states.

Current guidelines on prophylactic iron supplementation are 60-120 mg elemental iron/d. Lower dosages appear to be less effective. At dosages of ≥120 mg/d, adverse reactions increase and adherence is poor.[62]

The hemoglobin concentration usually measured in isolation shows a poor correlation with iron stores, so ferritin level must guide iron supplementation. Ferritin levels of <70 g/L at the start of pregnancy are indicative of subsequent iron deficiency. Due to individual variation in iron metabolism during pregnancy, the best time for measuring iron stores is unclear.[53]

Treatment of iron - deficiency anaemia in pregnancy

The method of treatment depend on various factors such as time until birth, severity of anaemia, additional risks, especially maternal comorbidities, and patients' preference.

Oral iron

This frontline therapy, has 70% incidence of significant gastrointestinal side effects (Table 7).[36] Constipation due to high progesterone levels and slow bowel transit worsened by the enlarging gravid uterus pressing posteriorly on the rectum is worsened by oral iron. Additionally, metallic taste and gastric cramping, further decrease adherence. Nonetheless, when tolerated, oral iron is effective, easy to obtain, and inexpensive. It is unclear whether weekly or intermittent administration of oral iron is equivalent to daily administration.[63] The ideal dosage is unknown because the proportional absorption is inversely proportional to the administered dose. Dosages between 100 and 200 mg daily are a compromise in relation to the hemoglobin increase and tolerability of iron. The recommended dosage is 80-160 mg elemental iron/d.

As a response to oral iron, reticulocytosis occurs within 3 to 5 days and increases until 8 to 10 days after treatment. The hemoglobin increase follows after a delay and is, at best, approximately 0.2 g/dL per day or approximately 2.0 g/dL within 3 weeks. Once the hemoglobin levels have returned to normal, oral iron should be continued for at least another 4 to 6 months until a target ferritin level of approximately 50 ng/mL and a transferrin saturation of at least 30% have been reached.[61]

In event of adverse event, the dose must be either reduced or switched to a different formulation. Unfortunately, no formulation has shown superiority over another in prospective studies and adherence continues to be a problem. (Table 7)

Parenteral iron Formulations

Parenteral iron circumvents the natural mechanism of iron absorption via the intestine and facilitates transferrin saturation. Free iron is toxic because it promotes the formation of

hydroxide and oxygen radicals, which in turn result in cell and tissue damage via peroxidation. Newer formulations, which bind elemental iron more tightly to the carbohydrate core, limit the amount of labile free iron released, thus minimizing reactions and serious adverse events.[64] In a meta-analysis minor infusion reactions were observed.[65] Gastrointestinal toxicity was rare.

Intravenous iron sucrose complex too is safe and effective in pregnancy and postpartum, and its side effect profile is better than oral iron.[44],[66],[67] However, because the sucrose moiety binds elemental iron less tightly, doses between 200 and 300 mg are proscribed.[68]

Recently iron sucrose complex has been substituted by FCM complex, whose carbohydrate moiety binds the elemental iron more tightly. This allows high dosages up to 1000 mg/administration over a short period (15 minutes). FCM does not cross the placenta in a placenta-perfusion model but has fewer side effects than iron sucrose, despite a considerably higher single dosage.[69]

In contrast to high-molecular-weight dextran-containing preparations, which are no longer available, LMW ID is safe and effective in gynecologic patients without any reported serious adverse events in published studies.[70],[71]

Iron deficiency anaemia in children

Overt clinical signs and symptoms are not observed in most infants and children with mild anaemia. Initial evaluation include a thorough history regarding prematurity, low birth weight, diet, chronic diseases, family history of anaemia, and ethnic background. A complete blood count is the most common initial diagnostic test used to evaluate for anaemia. It allows for differentiating microcytic, normocytic, and macrocytic anemia based on the mean corpuscular volume.

Diagnosis of Iron deficiency anemia

Every child with history of poor dietary iron intake should receive a trial of iron supplementation and dietary counseling. Anaemia, defined as a hemoglobin level two standard deviations below the mean for age, is prevalent in infants and children worldwide.[72] Iron deficiency anaemia is likely if the hemoglobin level increases by more than 1.0 g per dL (10 g per L) after one month of presumptive treatment. The most common type of anaemia in children is microcytic anemia due to iron deficiency with prevalence of 1% to 2% in U.S. children of one to five years. The expected microcytic, picture if replaced with normocytic red blood cells or if suspected iron deficiency anemia does not respond to treatment, ferritin measurement is the most sensitive test. Ferritin is a good reflection of total iron storage and is also the first laboratory index to decline with iron deficiency. It may be less accurate in children with infectious or inflammatory conditions because ferritin is also an acute phase reactant. An elevated red

Table 7: Conditions with low or limited response to oral iron preparations

- Noncompliance
- Severe side effects (e.g., gastrointestinal)
- Limited absorption (e.g., in inflammatory bowel disease)
- Postoperative phase (first days to weeks)
- Abnormal hepcidin regulation
- Limited time
- Chronic inflammatory stages (e.g., rheumatoid arthritis)
- Use of red cell–stimulating hormones (e.g., rhEPO, NESP)
- Preexisting moderate-to-severe iron-deficiency anemia
- Iron preparation with low pharmacological properties
- NESP, novel erythropoiesis stimulating protein; rhEPO, recombinant human erythropoietin

blood cell distribution width index is an alternative sensitive test to differentiate iron deficiency anaemia from other types of microcytic anaemia.[72]

Table 8: Conditions favouring the use of intravenous iron for anaemia therapy in pregnancy

- Preexisting anemia (moderate to severe)
- No effect of oral iron (low resorption)
- Side effects of oral iron (poor compliance)
- Refusal of blood transfusion
- Limited time until delivery or planned operation
- Coexisting risks (e.g., placenta previa, Jehovah's Witness)
- Preoperative and postoperative phases

Prevention of iron deficiency anaemia

During pregnancy and delivery

Up to 42% of pregnant women worldwide will have anaemia. The iron requirement increases with each trimester and should be supported by higher maternal iron intake. Between 60% and 80% of the iron storage in a newborn occurs during the third trimester but it is unclear whether treatment of maternal anaemia prevents anaemia in newborns and infants, 15 and statistically significant benefits in clinical outcomes (e.g., low birth weight, preterm birth, infection, postpartum hemorrhage) for mothers or newborns.[72]

Delayed umbilical cord clamping (approximately 120 to 180 seconds after delivery) is associated with improved iron status (ferritin levels) at two to six months of age. It is especially important for premature or small for gestational age infants, who are vulnerable to iron deficiency. But its effect do not appear to persist beyond the first 12 months. [72]

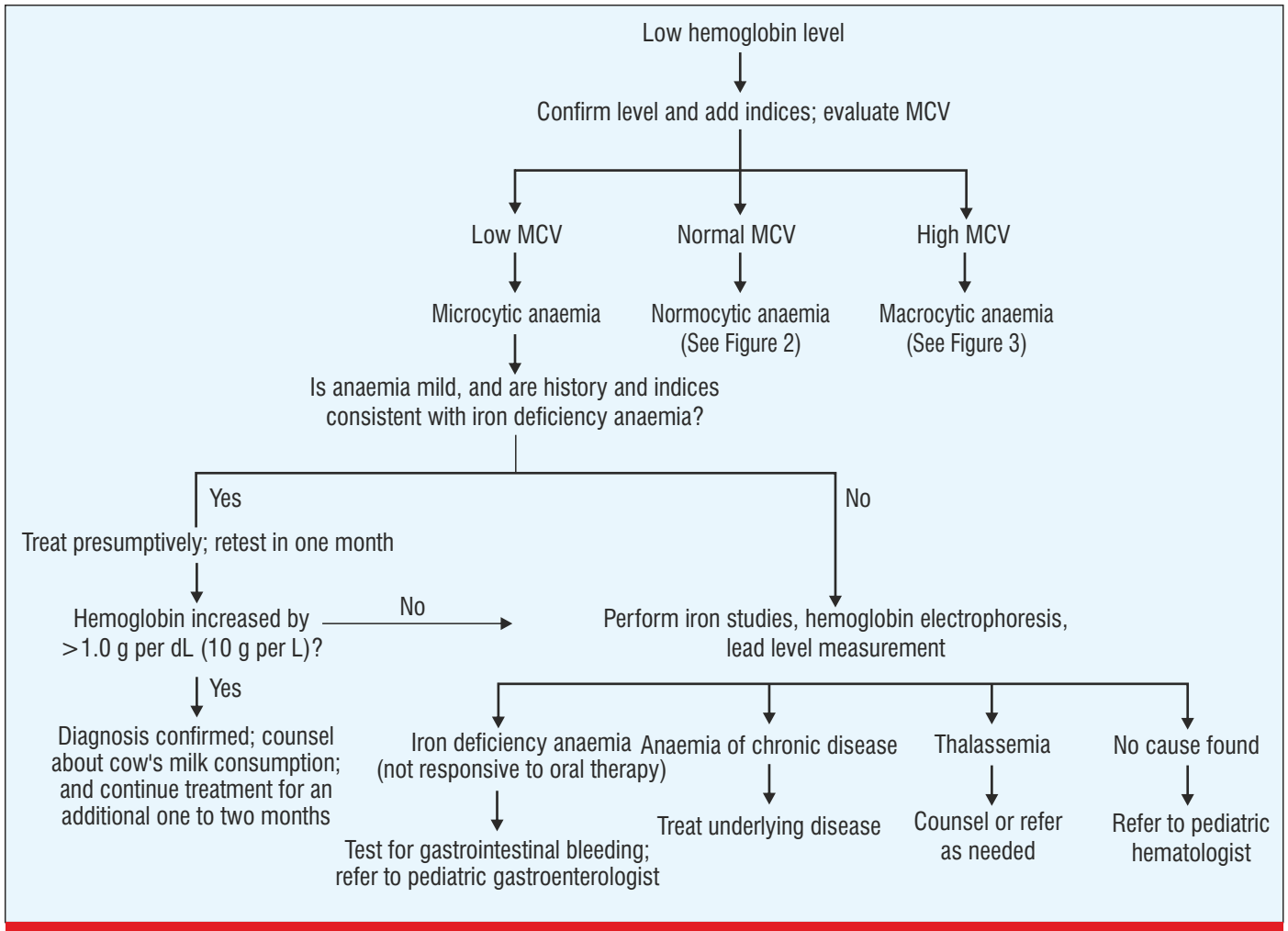

Figure 6: An algorithm for the evaluation of children with low hemoglobin levels (72)

In healthy full-term infants, iron storage from in utero is adequate for the first four to six months of life. Iron is the most common single-nutrient deficiency. The AAP recommends that full-term, exclusively breastfed infants' start 1 mg per kg per day of elemental iron supplementation at four months of age until appropriate iron-containing foods are introduced. Formula-fed infants often receive adequate amounts of iron (average formula contains 10 to 12 mg per L of iron) and thus rarely require further supplementation. Preterm infants (born at less than 37 weeks' gestation) who are exclusively breastfed should receive 2 mg per kg per day of elemental iron supplementation from one to 12 months of age, except for those who have had multiple blood transfusions. Daily iron supplementation and requirements for children is summarized in Table 10.

Clinical impact of iron deficiency

Several symptoms of iron deficiency can manifest even in the absence of progression to anemia. While some are likely to be caused by iron deficiency (e.g., pagophagia, and RLS); many symptoms are nonspecific (fatigue, and exhaustion). It hinder the diagnosis and the condition is left untreated. In populations where iron deficiency is highly prevalent, appropriate diagnostic tests can be performed for such symptoms and if necessary, treatment can be given. In this section, the iron deficiency in patients with CHF, CKD and IBD is discussed.[7

Iron deficiency in chronic heart failure

Chronic heart failure (CHF) has 37-61% prevalence of iron deficiency, which increase as CHF advances.[73] Its multifactorial etiology is not fully understood, but is postulated as: a general loss of appetite and poor nutrition; decreased gastrointestinal (GI) iron absorption due to edema; increased GI blood loss that may occur partially as a result of antiplatelet and anticoagulant drugs; and, importantly, as a consequence of the chronic inflammatory state of these patients.[74],[75] Due to overlapping key manifestations of ID and CHF (fatigue, reduced work capacity, and exercise intolerance); the diagnosis of ID in CHF patients is complicated. Fatigue is significantly more frequent if CHF patients have iron deficiency, [76] as proved by 6 min walk test (6MWT) and exercise-induced symptoms.[77] In the FAIRHF and recent EFFECTHF study, iron-deficient CHF patients who were treated for iron deficiency with intravenous (IV) iron, ferric carboxymaltose, had significant improvements in the 6MWT compared with those receiving placebo.[78]

The QoL (Quality of Life) is significantly affected by iron deficiency in patients with CHF. Iron deficiency can also negatively impact outcomes and increased mortality (by 40-60%) in

Table 1: Age-Based Hemoglobin Levels in Children and Adolescents (72)

Age	Mean hemoglobin level	−2 Standard deviations
Birth (term infant)	16.5 g per dL (165 g per L)	13.5 g per dL (135 g per L)
1 month	13.9 g per dL (139 g per L)	10.7 g per dL (107 g per L)
2 months	11.2 g per dL (112 g per L)	9.4 g per dL (94 g per L)
3 to 6 months	11.5 g per dL (115 g per L)	9.5 g per dL (95 g per L)
6 months to 2 years	12 g per dL (120 g per L)	10.5 g per dL (105 g per L)
2 to 6 years	12.5 g per dL (125 g per L)	11.5 g per dL
6 to 12 years	13.5 g per dL	11.5 g per dL
12 to 18 years		
Males	14.5 g per dL (145 g per L)	13 g per dL (130 g per L)
Females	14 g per dL (140 g per L)	12 g per dL

CHF.[79],[80],[81] The risk of hospitalization doubled in patients who were not treated for ID compared to those who were (IV ferric carboxymaltose),[82] proved by CONFIRM HF study.[77] The benefit of treating ID is notable irrespective of anaemia, thus establishing ID as an independent therapeutic target in CHF.[83],[84] Thus compulsory iron deficiency screenings and treatment with IV iron (e.g., ferric carboxymaltose) has been recommended in patients with CHF.

Iron deficiency in chronic kidney disease

The incidence of ID with CKD range from 24-85% and, increases as CKD progresses.[85],[86] The associated causes are: decreased GI iron absorption, malnutrition and blood loss, which is worsened by chronic inflammation.[87] Blood loss in CKD patients can originate from ongoing assessment tests and treatments such as dialysis. Additionally, iron utilization is promoted during the use of erythropoiesis stimulating agents (ESAs). ESA therapy, while effective in correcting anaemia, can further exacerbate iron deficiency, which in turn may result in poor response to ESAs.[88] Unlike cardiologists, nephrologists do not recognize iron deficiency, which is easily treatable, as a distinct entity and still aim to treat iron deficiency in the context of anaemia management. Thus, in contrast to CHF, where there is strong evidence that iron deficiency alone impacts the underlying disease, the evidence in CKD is almost non-existent and focuses only on anaemia, of which iron deficiency is a major cause.

Anaemia in CKD is frequently associated with reduced QoL, particularly in physical domains such as vitality and energy. Similar to CHF, these physical domains appear to play a major role in patient QoL. This is supported by data demonstrating that normalization of hemoglobin (Hb) levels is associated with significant improvements in physical function.[89]

At present, the major importance of iron deficiency in CKD is its role in the development of chronic anaemia, which is easily correctable. Anaemia in CKD is associated with an increased risk of morbidity and mortality.[90] In non-dialysis CKD patients, lower time-averaged Hb levels correlated with a significantly increased risk of predialysis mortality and end-stage renal disease.[90] In a 5 year observational study, anaemia in CKD patients was again associated with increased mortality, regardless of CKD severity.[91] The change from baseline to follow-up in the prevalence of anaemia was much higher in patients with CKD stage 2 and 3 who died compared with those who were alive at the end of observation[91] Notably, one study demonstrated that ESA treatment for the correction of anaemia in patients with type 2 diabetes and CKD had significant safety concerns, (e.g., stroke).[92] Moreover, no overall cardiovascular, renal or QoL benefits were observed when targeting higher Hb levels compared with the placebo group, who received only iron.[92] This further supports the point of treating iron deficiency prior to anaemia development and requirement for ESAs.

Anaemia in CKD patients is often associated with cardiovascular morbidities and can result in increased hospitalization,[93] leading to cardio-renal-anemia syndrome. While this overlap between CKD and CHF populations is recognized, the nature of cardiac disease may differ between these groups. As there are differences in the nature of the heart failure, the consequences and treatment of iron deficiency may also differ.

Iron deficiency in inflammatory bowel disease

ID affects 13-90% of patients with IBD, depending study population (in or outpatients, active or quiescent), as well as severity of the disease.[85] The etiology of ID in IBD is; impaired GI iron absorption due to chronic inflammation, bowel resection (especially in Crohn's disease), disease triggered malnutrition and (mainly chronic) blood loss.[94] As with nephrologists, not all

gastroenterologists fully appreciate the importance of managing iron deficiency. The role of iron deficiency anaemia in IBD is undervalued.(94) ID is the most common complication and extra-intestinal manifestations of IBD, though over 50% of patients of them are not treated for anaemia.[95] The chronic fatigue is associated with impaired QoL in anaemic IBD patients, along with abdominal pain and diarrhea.[96] Notably, improvements in iron status with IV iron treatment have led to significantly improved QoL in patients with ulcerative colitis and Crohn's disease. The IBD QoL questionnaire improved with changes in Hb levels (but not the activity of the underlying disease).[97]

Table 10. Elemental Iron Supplementation or Requirement in Children

AGE	IRON SUPPLEMENTATION OR REQUIREMENT
Preterm (< 37 weeks' gestation) infants: 1 to 12 months	2 mg per kg per day supplementation if exclusively breastfed
	1 mg per kg per day supplementation if using iron-fortified formula
Term infants: 4 to 6 months to 12 months	1 mg per kg per day supplementation if exclusively breastfed
	Supplementation not needed if using iron-fortified formula
Toddlers 1 to 3 years	Requires 7 mg per day; modify diet and/or supplement if anaemic
Children 4 to 8 years	Requires 10 mg per day; modify diet and/or supplement if anaemic

a. Guidelines that only report diagnosis thresholds specific to IDA have been described as 'IDA only'

b. Includes both haemodialysis and non-dialysis chronic kidney disease

c. These threshold values are based on target ranges for the treatment of iron deficiency

d. Possibly more, depending on degree of inflammation. ACCF, American College of Cardiology Foundation; AHA, American Heart Association; AID, absolute iron deficiency; CRP, C-reactive protein; ECCO, European Crohn's and Colitis Organisation; ERBP, European Renal Best Practice; FID, functional iron deficiency; IBD, inflammatory bowel disease; ID, iron deficiency; IDA, iron deficiency anaemia; KDIGO, Kidney Disease Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; KHA-CARI, Kidney Health Australia-Caring for Australiasians with Renal Impairment; NCGC, National Clinical Guideline Centre; NICE, National Institute for Health and Care Excellence; NZ, New Zealand; SF, serum ferritin; sTfr, soluble transferritin receptor; TSAT, transferrin saturation

Diagnosis of iron deficiency in chronic inflammatory conditions

Available international guidelines for CHF, CKD and IBD reveals no consensus practical guidance for diagnosing iron deficiency independent of anaemia (Table 11) and only some recognize iron deficiency as a standalone condition. ID can be simply diagnosed with routinely available blood tests measuring serum ferritin and transferrin saturation (TSAT), [98] yet test cut-off values are not in agreement.[85] Serum ferritin levels being sensitive to inflammation; some guidelines recommend assessment of chronic inflammation (Creactive protein [CRP] and erythrocyte sedimentation rate). Even no standard CRP cut-off values (threshold 5 mg L-1) are provided.[99]

Expert recommendation

The guidelines on how iron deficiency in the absence of anaemia should be diagnosed in relation to the underlying chronic disease, provide no direction. Thus, it is of little surprise that physicians may not prioritize iron deficiency treatment. The consensus laboratory test cut-off

values in patients with CHF, CKD or IBD are:

Serum ferritin <100 g L−1or TSAT <20%

If serum ferritin is between 100 and 300 g L−1, a TSAT test will be required to confirm iron deficiency

Furthermore, algorithms for the diagnostic work-up of iron deficiency in patients with CHF, CKD, and IBD are available. In all conditions, initial work-up incorporate assessment of serum ferritin and TSAT, as well as Hb levels. In addition to laboratory report whether CKD patient is receiving dialysis, and IBD case is in remission or active, should be taken into account. For IBD, stool markers such as calprotectin or lactoferrin, transabdominal ultrasound or endoscopy, may also be used to supplement these assessments.

Iron deficiency in high - risk populations with chronic inflammatory conditions

Chronic conditions further increase susceptibility to iron deficiency. To optimize outcomes consider three important populations: women (menorrhagia, pregnant or are planning to become pregnant); elderly; and those undergoing surgery. 4-52% of women of reproductive age are reported to suffer from heavy menstrual bleeding, and consequent ID and iron deficiency anaemia. (100) It affects QoL and well-being of the sufferer.[47] Many women enter pregnancy with low iron stores and are often already anaemic leading to a serious detrimental effect on the outcome for both mother and child.[101] The increased maternal morbidity and mortality is possibly due to not being able to withstand the adverse effect of excessive blood loss at delivery and the increased risk of infection. Whereas the child has increased risk of preterm labor and subsequent low birthweight, and perinatal complications,[102] as infants born to anemic mothers being more likely to be anemic themselves.[103] Iron deficiency also carries negative long-term impact on the mother–child relationship and the child's cognitive development.[104],[59]

Elderly patients have prevalence of iron deficiency increasing rapidly with age, and timely diagnosis and treatment may improve QoL and outcomes for multiple comorbidities.[104] Regardless of age, ID has potential impact during procedure that result in major blood loss; so it has to be recognized early and pro-actively managed. An awareness of the substantial

			Recommended iron deficiency threshold values independent of anemia		
Professional association	Year	ID/IDA[a]	Serum ferritin (mg L−1)	TSAT (%)	Additional tests
Chronic heart failure					
ACCF/AHA	2017	ID and IDA	<100 or 100–300	– and <20	–
Canadian Cardiovascular Society	2014	IDA only	–	–	–
European Society of Cardiology	2016	ID and IDA	<100 or 100–299	– and <20	–
French cardiologists	2014	ID	AID<100; FID 100-299	– and <20	–
German commentary for European Society of Cardiology	2013	ID	<100 or 100-299	– and <20	–

National Heart Foundation of Australia and Cardiac Society of Australia and NZ	2011	ID	No threshold recommended	No threshold recommended	–
Spanish Society of Cardiology and Spanish Society of Internal Medicine	2017	ID	<100	or <20	If patients have SF <100 mg L^{-1} but TSAT >20%, test for sTfr
Chronic kidney disease[b]					
Canadian Society of Nephrology	2008	IDA only	–	–	–
ERPB	2013	ID and IDA	AID<100	and<20	–
KDIGO	2012	IDA only	–	–	–
KDOQI	2012	IDA only	–	–	–
KHA-CARI[c]	2013	ID	<100;<200-500	<20;<20-30	
NCGC	2015	IDA only	–	–	–
UKNICE	2015	IDA only	–	–	–
UK Renal Association	2012	IDA only	–	–	–
Inflammatory bowel disease					
Quiescent IBD					
ECCO	2015	ID and IDA	<30	–	–
Portuguese Working Group on IBD	2016	ID and IDA	<30	and <16	CRP assessments
Active inflammatory bowel disease					
British Society of Gastroenterology	2011	ID and IDA	<50[d]	–	–
ECCO	2015	ID and IDA	<100	–	–
Portuguese Working Group on IBD	2016	ID and IDA	30-100	and <16	CRP assessments

Table 11: IDA has more guideline coverage than ID: summary of ID diagnostic measures, independent of anaemia

impact of pre-operative iron deficiency with and without anaemia on morbidity and mortality is increasing, with growing recognition that patient blood management procedures need to be established across all surgical specialties.[28]

Management of iron deficiency in chronic inflammatory conditions

Widely implied oral iron treatment is convenient, but its limitations impact effectiveness in

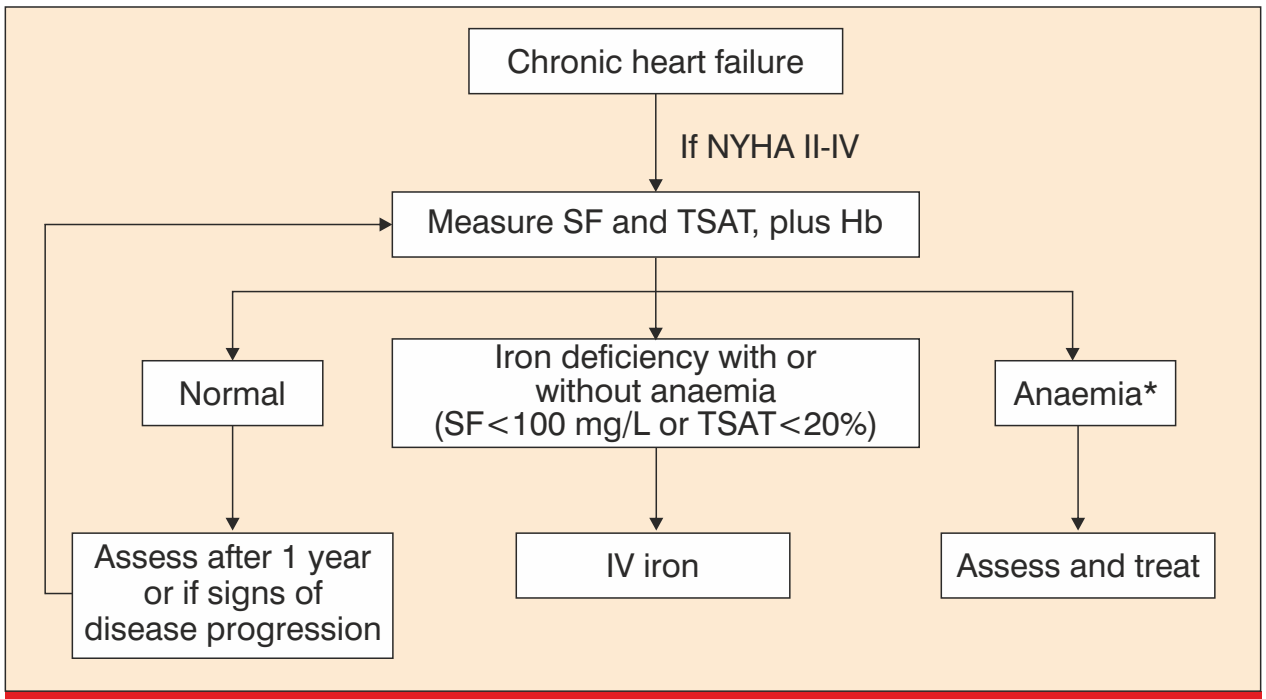

Figure 7: Diagnostic algorithm: iron deficiency in chronic heart failure

patients with chronic inflammatory conditions. On average 10% of ingested iron is biologically available and even in iron-deficient conditions, upregulation of absorption may be limited.[105] During active inflammation, absorption is further reduced as a result of hepcidin-mediated ferroportin inhibition[106] Recent evidence from the IRONOUT study further supports the ineffectiveness of oral iron in chronic disease, CHF and CKD.[107] Moreover, oral iron significantly changes normal gut microbiota, leading to well-known GI intolerance, particularly detrimental to IBD patients.[108]

The alternative IV iron treatment, can deliver a larger iron supply, effectively replenishing iron stores due to route of administration, bypassing the risk of GI side effects. Many guidelines acknowledge the benefits of IV iron preparations as a valuable option. Patients of chronic inflammatory diseases particularly lack a response to, are non-compliant with, or are intolerant of oral iron treatment. They often have severe iron deficiency and require rapid replenishment of available iron and Hb levels. However, multiple IV iron preparations are available for which the dosing, infusion times, efficacy and safety profiles can vary and some products have very little data published demonstrating their benefit-to-risk profile. For ferric carboxymaltose, a wealth of clinical evidence on its use in all three chronic inflammatory conditions (CHF, CKD and IBD) is offered, supporting its effectiveness and good tolerability across patient groups.[109],[56]

Conclusion

Iron deficiency anaemia is arises when the balance of iron intake, iron stores, and the body's loss of iron are insufficient to fully support production of erythrocytes. It has significant impact on human health. Although it can easily identified and treated, but frequently overlooked by physicians. The underlying cause of IDA should be treated, and oral iron therapy should be initiated to replenish iron stores. Parenteral therapy may be used in patients who cannot tolerate or absorb oral preparations. Overall, the prevention and successful treatment for iron deficiency anaemia remains woefully insufficient worldwide, especially among underprivileged women and children.

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Dear Doctor,

Iron is an essential micronutrient required for several functions in human body. It is required for cellular growth and differentiation, oxygen binding, transport and storage, enzymatic reactions, immune function, cognitive function, mental and physical growth etc. Therefore, deficiency of iron due to either physiological or pathological reason has adverse impact on mental and physical growth resulting in decreased learning capacity and work productivity in children. Iron-deficiency anaemia (IDA) is a problem of major public health significance. In India, the burden of IDA is 3.0 times higher than the average globally for other geographies at a similar level of development, and that women and children are disproportionately affected.

It is indeed a pleasure to present to you this QMR issue by Dr. K Janardan Trusty, renowned pediatrician. In this issue, he is enlightening us on 'Iron Deficiency Anaemia - Clinical Implications & Management'.

I sign off by once again reminding you to continue sending in your comments and suggestion regarding the QMR. Do write to me at balaji.more@raptakos.com with your write ups, notes or tidbits on various topics of interest that can make for informative and interesting reading.

With best regards,

Dr. Balaji More
Vice President - Medical

Feedback form: July - September 2019
Iron Deficiency Anaemia - Clinical Implications & Management

1. Your comments on this issue of Q.M.R.

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2. Please suggest medical topics for our QMR which could be printed in future.

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