CHAPTER 21

Iron therapy

Carlo Brugnara, Photis Beris

1. Introduction

"*Iron deficiency is the most common cause of anaemia worldwide*". This sentence, repeated in a large number of publications and textbooks, highlights the health relevance of iron deficiency and the need for proper treatment, in conjunction with the elimination of the underlying conditions causing this disease. Food supplementation, proper nutrition and sanitation have reduced the prevalence of iron deficiency in developed nations, while in under-developed or developing countries estimates of the prevalence of iron deficiency have ranged from 30 to 70% (1). Chapters 19 and 20 of this textbook provide an excellent overview of iron metabolism, its controlling mechanisms and alterations, and the effects of these alterations on erythropoiesis.

Iron deficient states may develop due to unmet increased metabolic iron requirement or inadequate supply states, or both. Due to the extreme dependence of iron metabolism on "recycling" of the iron contained in the aged red cells, excessive blood loss is one of the most common conditions producing iron deficiency: blood loss may be gastrointestinal, genital in women, urinary, and rarely respiratory. Frequent blood donations should be kept in mind as a cause of iron deficiency. In addition, pregnancy in women (2) and growth in children (3, 4) are two physiological conditions which increase iron requirements and are frequently associated with iron deficiency. Table 1 outlines the most common physiological conditions with a high likelihood to produce an iron deficient state requiring iron supplementation therapy.

A diet lacking the required amount of iron is a common cause of inadequate body iron supply. Even in developed countries, it has been shown that a large number of mothers do not appropriately supplement the diet of their breastfed infants with iron-containing foods (5).

A net loss of iron from the gastrointestinal tract can be produced by intestinal parasites (most commonly hookworms) (6) or by gastrointestinal pathologies, such as atrophic achlorydric gastritis, gastrointestinal surgery, and malabsorption syndromes.

Clinical presentations of iron deficient states cover a broad spectrum, from a

Table 1: **Physiological and pathological conditions with a high likelihood to require oral iron therapy**

Low-birth-weight infants
Infants and toddlers/young children (6 months to 2 years)
Adolescent girls
Pregnancy
Menstruating women, especially when a history of abundant blood loss is present
Long-distance runners and other endurance sports

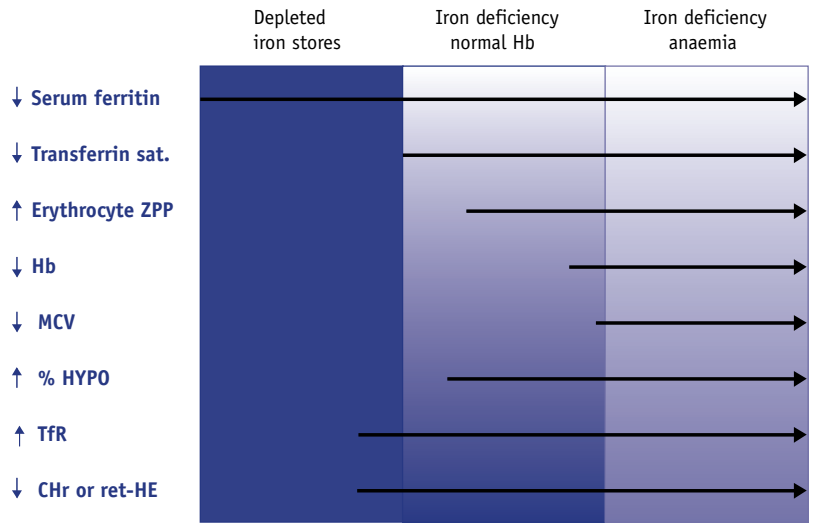
casual finding of laboratory abnormalities at a routine screening in the absence of symptoms to profound iron deficiency anaemia with pica. Of particular clinical and epidemiological importance are iron deficient states developing in infants and toddlers, since they are likely to result in permanent alterations of cognitive development and intellectual functions, which cannot be reversed by iron supplementation therapy (7-12).

2. Diagnosis of iron deficiency

Iron deficiency has been classically been defined in 3 progressive states (13) (see Figure 1):

a. *Storage iron depletion*: this state can be identified only on the base of an abnormally low level of serum ferritin: a level below 12 µg/L is considered by many as diagnostic of depleted iron stores. At these early stages, no haematological changes are apparent, Hb and red cell indices are still within the normal range (14). It is likely that abnormally low serum levels of hepcidin will

Figure 1: **Stages of iron deficiency**



Alterations in biochemical and haematological parameters at various stages of iron deficiency. Transferrin sat.: serum transferrin saturation; ZPP: zinc protophorphyrin; Hb: haemoglobin; MCV: mean corpuscular volume; % HYPO: % hypochromic erythrocytes; TfR: serum transferrin receptor; CHr or ret-HE: reticulocyte haemoglobin content.

be an important indicator of this early stage of iron deficiency (15).

b. *Iron deficiency with no anaemia*: at this stage, the Hb level is still normal, but other biochemical and haematological signs begin to appear, such as reduced serum transferrin saturation, increased circulating serum transferrin receptor (TfR), elevated erythrocyte zinc protoporphyrin, increased % of hypochromic erythrocytes, and abnormally low reticulocyte Hb content (CHr or ret-HE) (16).
c. *Iron deficiency anaemia*: the classical biochemical signs of iron deficiency are accompanied by the haematological changes characteristic of iron deficient erythropoiesis, with anaemia, decreased MCV, MCH, and reticulocyte Hb content, and increased RDW (17).

The differential diagnosis of microcytic hypochromic anaemia should take into consideration thalassaemias, especially beta-thalassaemia trait and two gene alpha-thalassaemia trait. A very useful parameter in distinguishing iron deficiency from thalassaemias is the micro/hypo ratio (18), which is usually >1.0 in thalassaemia, where microcytosis prevails, and <1.0 in iron deficiency, where hypochromia is more pronounced. Other haemoglobinopathies with microcytosis, and congenital or acquired disorders of haem synthesis (sideroblastic anaemias) should also be considered in the differential diagnosis.

3. Oral iron therapy

Oral iron supplements are an inexpensive and effective way of treating the vast majority of iron deficient states. However, it is important to consider that duodenal absorption of iron is limited: under normal steady-state conditions, approximately 10% of the ingested non-haem iron is absorbed by the duodenum (~ 1 mg/day). Duodenal absorption of iron is increased in iron-deficient states (19), however it is generally assumed that 25 mg of elemental iron is sufficient to essentially saturate the duodenal absorptive capabilities. Oral iron therapy is usually best carried out in 3-4 divided doses per day, with a total of 150-200 mg of elemental iron for adults or 6 mg iron/kg body weight in children. It has also been suggested that attempts be made to individualise treatment and get patients more involved in determining the most tolerable daily iron dose, its formulation and its schedule. This can be best accomplished by basing therapy on monthly cycles of 5,000 mg of ingested elemental iron (20). Given the toxicity of large doses of iron, it is essential that iron supplements be kept in a safe place not accessible to young children.

Several different preparations are available for oral iron supplements. These preparations contain either the iron ferric or the iron ferrous salt forms, which are formulated in various preparations (amino-acid chelates, carbonyl iron, polysaccharide-iron complex, combination products, extended-release products, etc.; see Table 2) (21). Ascorbic acid and iron combinations are also available, since

Table 2: **Oral iron formulation**

Formulation	% Elemental iron (w/w)
Carbonyl iron	100
Ferric ammonium citrate	18
Ferric bisglycinate	20
Ferrous fumarate	33
Ferrous gluconate	12
Ferrous sulfate	20
Ferrous sulfate, dried	30
Haem-iron peptide	100
Polysaccharide-iron complex	100
Controlled release	31

Adapted from (21).

it has been shown that ascorbic acid promotes duodenal iron absorption (22). Phytate is a well known inhibitor of iron absorption (23). Iron needs to be in the ferrous form to be absorbed by the intestinal mucosa, while ferric forms need to be reduced to ferrous for optimal absorption. Since food can decrease absorption of iron up to 50%, iron supplements should ideally be taken with an empty stomach. Haem-iron preparations are also available: this form of iron is better absorbed that iron salts, but it is derived from animal sources and thus in many countries it is considered a "medical food" rather than a dietary supplement (21).

The most common causes for partial response or unsatisfactory response to oral iron are listed in Table 3. However, there have been only a handful of properly controlled studies to assess differences in side effects between different oral iron formulations: these studies reported a lower incidence of side effects for controlled release and polysaccharide iron complex preparations, but these differences did not result in significantly different therapy discontinuation rates (24, 25). Gastrointestinal side effects are the most frequent side effects reported for oral iron therapy, and may affect up to 20% of patients. In addition to diarrhea or constipation, upper gastrointestinal symptoms include nausea, abdominal discomfort/pain, and more rarely vomiting. The symptoms appear mostly in the first hour after the ingestion of iron supplements and may be alleviated by a reduction in the dose. Symptoms may also be alleviated by taking the iron supplements with food, but this will result in a lower rate of body stores repletion. Mucosal deposition of iron has been demonstrated in patients taking oral iron supplements, but mucosal disruption and erosions were only noted in the esophagus and stomach and not in the duodenum (26).

Table 3: **Causes of treatment failure in oral iron therapy**

Lack of adherence to therapy or insufficient length of therapy for the degree of iron deficit
Concomitant/causal underlying blood loss pathology not resolved
Poor duodenal absorption: • Concomitant GI pathology (inflammatory bowel disease or any other cause or chronic inflammation; malignancy) • Insufficient gastric acidity (pharmacological blockade of gastric secretion) • Chemical inhibition of absorption (lead-aluminum)
Side effects: • Nausea • Constipation • Upper GI irritation
Iron-refractory iron deficiency anaemias (IRIDA)

Patients should be reminded that oral iron supplements produce black or dark green stools.

Oral iron therapy should not be considered for patients on haemodialysis therapy and cancer patients receiving erythropoiesis-stimulating agents (ESA). Several studies showed increased efficacy of ESA in cancer patients with the addition of intravenous (IV) iron (27-29). A recent meta-analysis study showed the superiority of IV iron compared with oral iron in Hb response (30). IV iron therapy has also been shown to be superior to oral iron in reducing fatigue and replenishing iron stores in post-partum anaemia (31, 32). However, there is a need for well-conducted and controlled clinical trials to assess benefits and side effects of iron therapy in the anaemia of pregnancy (33, 34). In inflammatory bowel disease, the impaired intestinal absorption of iron (35) and the possibility that iron may further damage the intestinal mucosa should prompt serious considerations for the use of IV rather than oral iron therapy (36), although more studies are needed in this area as well (37). Patients undergoing colorectal cancer surgery have been shown to particularly benefit from a two-week preoperative oral iron supplementation therapy with a significant reduction in allogeneic blood transfusion requirements.

3.1 Treatment monitoring

In the absence of underlying diseases, which cause either substantial blood loss or impair intestinal iron absorption, it is generally assumed that oral iron replacement therapy should produce a noticeable change in Hb levels in 2-3 weeks and Hb levels should approach the steady state in 2 months. An early change in reticulocyte

absolute count and reticulocyte Hb content can be appreciated as early as one week after initiation of oral iron therapy (38). Therapy should be continued for a few months after the desired change in Hb levels is achieved, to guarantee adequate replenishment of body iron stores. For severe cases of iron deficiency, therapy may be needed for at least 6 months and up to one year.

In addition to Hb, haematological parameters such as reticulocyte count and reticulocyte Hb content (39) are helpful in assessing the extent of the response to oral iron and to identify either poor adherence to treatment or concomitant pathology which limits the effect of oral iron (17, 39, 40).

Biochemical parameters are less helpful, since plasma iron levels are highly variable, and may be in the normal range just because a single iron pill was taken before the blood draw. However, recent evidence suggests that it is possible to use changes in serum iron following the administration of oral iron supplements to determine iron absorption (41). Serum ferritin is a more valuable parameter, since it is not influenced by daily variations in iron intake. A progressive rise in serum ferritin (in the absence of inflammation) is a sign that the patient is adhering to the therapy and that iron is effective in replenishing the body stores. However, ferritin is one of the last parameters to normalise because it usually begins to increase only after the anaemia is corrected.

Serum transferrin receptor is another biochemical marker of iron status which shows changes with iron therapy. A plot which combines sTfr/log ferritin ratio and CHr (Thomas plot) has been shown to provide useful information in characterising iron deficient states and the effects of iron replacement therapy in both adults and very low birth weight infants (42-44).

Treatment failures are usually due to poor compliance or to the persistence of the underlying pathology, such as an ongoing blood loss, which is not matched by the increased erythropoiesis. Additional pathologies which may contribute to poor therapeutic response to oral iron can be gastrointestinal (poor absorption), systemic (acute or chronic inflammation/infection, cancer), and due to concomitant deficiencies (copper, folate, vitamin B12, inappropriately low erythropoietin production). Chronic lead poisoning may also limit the response to oral iron therapy. In elderly patients, hypochlorhydria or achlorhydria are a frequent cause of poor therapeutic response.

Physicians should consider rare genetic anaemias as cause of treatment failures. It has recently been shown that familial forms of iron deficiency anaemia which are refractory to oral iron therapy and poorly respond to IV iron, are associated with specific defects in TMPRSS6, a type II transmembrane serine protease produced by the liver which regulates the expression of hepcidin (45).

In selected cases, studies measuring serum iron levels following a test dose of oral iron may be helpful in identifying problems with intestinal absorption. Studies in normal subjects have shown that the % absorption of a 100 mg Fe dose can vary in normal subjects from 4.9 to 26.8% with an average value of 14.7±6.2 (SD, n=11) (41).

4. Intravenous iron therapy

As outlined in the first part of this chapter, oral iron supplementation is efficacious in treating the vast majority of cases of iron deficiency anaemia, the most common kind of anaemia worldwide (46). In this section we will review established indications for IV iron administration, we will describe how this therapy should be given, we will present the existing iron preparations for intravenous use, their specificities and most important we will discuss safety of IV iron infusion.

4.1 Indications for intravenous iron treatment

IV iron administration is indicated in four situations:

a. In acquired or hereditary decreased intestinal iron absorption and/or liberation of iron from macrophages. Cases with high hepcidin levels secondary to any kind of inflammation represent the most common acquired cause of this setting (47). The newly described IRIDA disease is the best example of hereditary iron malabsorption associated with decreased iron release from the macrophages (48). This category also includes cases where, because of surgery, intestinal iron absorption is abolished, e.g. post gastrectomy.
b. In cases with true severe iron deficiency because of continuous severe iron bleeding (Rendu-Osler-Weber disease) (49) or because of increased iron needs (pregnancy) or combination of both previous situations (post-partum anaemia).
c. In cases of functional iron deficiency particularly when an erythropoietin stimulating agent (ESA) is used such as in renal anaemia, anaemia of cancer patients and autologous blood donation before elective surgery.
d. Finally in case of intolerance or non compliance to oral iron treatment.

We must keep in mind that in medical practice we often have mixed situations, e.g. a + b in inflammatory bowel disease or a + c in the anaemia of chronic renal insufficiency. Table 4 lists the main clinical indications for IV iron treatment.

4.2 How to administer intravenous iron

Infusion of iron can be given on an outpatient basis; however cardiopulmonary resuscitation equipment should be available. For this reason in many countries IV iron is only administered in hospitalised patients. Infusion should be given in peripheral veins and care should be taken to avoid chemical phlebitis at the

Table 4: **Main indications for IV iron treatment**
Cancer related anaemia
Post-partum iron deficiency anaemia
Anaemia of pregnancy
Anaemia of chronic kidney disease
Anaemia of inflammatory bowel disease
Anaemia in patients treated in an intensive care unit
To increase blood donation before surgery in elective orthopedic patients
In iron malabsorption syndromes (post gastrectomy, Biermer disease, IRIDA)
Intolerance of or non-compliance with oral iron treatment
Severe iron deficiency anaemia with continuous bleeding (Osler-Weber-Rendu disease)

infusion site. The dose of IV iron can be calculated in case of profound iron deficiency by using the formula:
Total iron deficit [mg] = body weight [kg] x (Target Hb – actual Hb) [g/L] x 0.24 + 500

In this formula Hb should be given in g/L (50). Depending the preparation used the above calculated amount of iron should be given as divided doses administered with 2-3 days interval or as a total unique dose. Iron dextran can be given as a "total dose infusion" provided a test dose of 25 mg dissolved in 100 mL isotonic saline had shown no adverse reactions (51). Ferric carboxymaltose (FeCarb) can be given up to 1000 mg per dose dissolved in 250 mL NaCl 0.9% over 15 to 30 min (52). Different schemes exist for treatment of anaemia in haemodialysis patients and for the treatment of anaemia of chronic diseases. We encourage physicians to respect administration instructions given by the manufacturer of each different iron preparation.

4.3 Available intravenous iron preparations (Table 5)

1. *High molecular weight iron dextran*, was for years considered to be the reference iron preparation for IV administration. The main advantage was the possibility to give the totality of the calculated iron dose. However, because of the antigenicity of the dextran macromolecule allergic reactions are the main severe complications which obliged clinicians to greatly limit its use (51). Currently high molecular weight dextran is only used in a few countries where the new IV iron preparations are not yet available.
2. *Low molecular weight iron dextran (Cosmofer®, Pharmacosmos, Holbaek, Denmark)* was recently introduced as an improved form of IV iron with a negligible risk of allergic reactions. Studies in pregnancy and in chronic kidney disease (53, 54) demonstrated its efficacy and its safety.
3. *Iron sucrose (Venofer®, Vifor, St. Gallen, Switzerland)* is one of the most popular

Table 5: **Comparison of the main commonly available IV iron preparations**

	High molecular weight iron dextran	Low molecular weight iron dextran	Iron sucrose	Ferric carboxymaltose
Antigenicity	increased, risk of allergic reactions	low	low or no	low or no
Total calculated dose may be given	yes	yes	no	do not exceed 1000 mg /dose
Duration of infusion	4-5 hours when the total dose is given	1 hour	30-45 minutes	15 minutes
Stability of the Fe carbohydrate complex	yes	yes	semi-labile	yes

IV iron preparations particularly in the treatment of renal anaemia (55). It was also studied in gynaecology, particularly in post-partum anaemia (56), in anaemia of inflammatory bowel disease (57) and in elective orthopedic surgery (58). It is administrated in doses varying from 50 to 300 mg/perfusion with a maximum dosage of 900 mg/week (= 3 x 300 mg). It is diluted in 1 mL 0.9% NaCl per mg of iron and it is given as an infusion over 15 to 45 minutes. The product is extremely safe, allergic reactions being < than 1/100.000 infusions.

4. *Ferric gluconate (Ferrlecit®, Schein, Pharmaceutical, Florham Park, NJ, USA)* is another IV iron preparation used in haemodialysis patients, in anaemia of cancer as well as in anaemia of patients treated in intensive care units. Because of stability of the molecule only small quantities of iron can be infused without risk of serious side effects (59, 60).
5. *Ferric carboxymaltose (Ferinject®, Vifor, St. Gallen, Switzerland)* is the most recently registred iron preparation in Europe. Clinical trials in chronic kidney disease, in the treatment of post-partum anaemia and in inflammatory bowel disease (61-63) have proved its efficacy and its safety. The most important advantages of this preparation are the possibility to infuse up to 1000 mg of iron, with almost no risk of side effects and in a small perfusion time (15 min).
6. *Ferumoxytol (AMAG Pharmaceuticals, Inc., Lexington, Massachusetts*) is an iron oxide nanoparticle with polyglucose sorbitol carboxymethylether coating designed to minimise immunological sensitivity so that large doses may be given (64). One phase 3 trial demonstrated the efficacy of this new agent in anaemic patients with chronic kidney disease.

4.4 Safety of intravenous iron administration

Gastrointestinal disorders (nausea, vomiting, abdominal pain, diarrhea or more often constipation) frequently observed in patients receiving oral iron therapy, are rarely seen with IV iron preparations with exception of the well-known metallic taste. The safety and tolerability of iron sucrose, low molecular weight iron dextran and ferric carboxymaltose is high. Hypersensitivity reactions (erythematous rash and urticaria) are rare and of mild or moderate intensity. The lack of recurrence after rechallenge indicates that in the majority of cases these events are not due to immunologic reactions to the previously mentioned IV iron preparations.

Severe life-threatening allergic reactions are a major problem with the high molecular weight iron dextran and this led to its progressive abandon in countries where the other preparations have been introduced (65).

Iron sucrose and iron gluconate are considered semilabile iron-sugar complexes and this explains the fact that some of the transfused iron binds to transferrin immediately after infusion, while ferric carboxymaltose and iron dextran are stable complexes that are taken up by macrophages before iron is released to transferrin and made available for erythropoiesis (63). This also underlines the need for repeated infusions of relative small doses /infusion and for a prolonged (>30min) infusion time. In fact complete transferrin saturation may lead to the presence of "free iron" which, being vasoactive, is responsible for anaphylactoid reactions (mainly severe hypotension) seen in patients where either high doses or rapidly iron sucrose is infused. Hypotension was also seen in 1% of patients treated with the very new iron preparation Ferumoxytol (19).

A few patients with ulcerative colitis treated with ferric carboxymaltose experienced tachycardia (63) and in 4% of patients treated with low molecular weight iron dextran flushing and palpitations were observed (64).

Cancer and anaemia of other chronic inflammatory diseases may be treated by the concomitant use of erythropoiesis stimulating agents and intravenous iron (27-29). In such cases the use of IV iron should be limited only in patients with suggestive functional iron deficiency (ferritin < 100 µg/L; transferrin saturation < 20%) (66) because long-term toxicities of IV iron remain largely undefined and unexplored. Transferrin oversaturation should be avoided as free – iron may enhance tumour growth (67) or exacerbate infections. In patients with chronic renal failure the problem of atherosclerosis and cardiotoxicity secondary to free radicals generated by "free iron" is still open.

In February 2008 a Drug Safety and Risk management Advisory committee of the US Food and Drug Administration Center for Drug Evaluation and Research drew attention to an increase in mortality among patients treated with intravenous ferric carboxymaltose (68). Five out of ten deaths after IV FeCarb were from cardiac causes

(69). In March 2008 the FDA requested safety data from additional clinical studies with the previously mentioned drug before definite approval of the drug in US (70).

5. Conclusions

Iron deficiency is the most common cause of anaemia worldwide. In the great majority of cases oral iron therapy represents an effective, inexpensive and safe way of treating this pathologic entity. There are however some specific situations where because of decreased or abolished duodenal iron absorption parenteral iron administration is mandatory. In the past IV iron preparations were considered dangerous because of the risk of life threatening allergic reactions. The introduction of new iron–carbohydrate complexes has eliminated this danger. As the organism possesses no mechanism for eliminating iron, when giving an IV iron preparation we must always calculate total iron needs to avoid iron toxicity secondary to iron overload. Finally when treating anaemia with iron, we must consider the possibility of erythropoietin deficiency which may in some cases explain the refractoriness of iron deficiency anaemia in IV iron administration. The same is true in functional iron deficiency states created by ESA monotherapy.

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Multiple Choice Questionnaire

To find the correct answer, go to http://www.esh.org/iron-handbook2009answers.htm

1. Which of the following is a known dietary inhibitor of gastrointestinal iron absorption:

a) Ascorbic acid ☐
b) Phytate ☐
c) Sugars ☐
d) Alcohol ☐

2. Please identify the laboratory parameter that changes late in the course of successful oral iron replacement therapy:

a) Reticulocyte count ☐
b) Hb ☐
c) Serum iron ☐
d) Ferritin ☐

3. Please identify the condition in which IV iron may be considered instead of oral iron due to poor GI absorption and to concerns about mucosal damage induced by iron:

a) Peptic ulcer ☐

b) Inflammatory Bowel Disease ☐
c) Colon cancer ☐
d) Diverticulitis ☐

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4. Please identify the intravenous iron form that has been consistently associated with severe adverse events including fatalities:

a) Iron sucrose ☐
b) Ferric carboxymaltose ☐
c) Low molecular weight iron dextran ☐
d) High molecular weight iron dextran ☐

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5. Please identify the intravenous iron form that can be infused in a total dose of up to 1000 mg in a short (15 min) infusion time:

a) Iron sucrose ☐
b) Ferric carboxymaltose ☐
c) Low molecular weight iron dextran ☐
d) High molecular weight iron dextran ☐

NOTES