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Chapter 1

Iron-Deficiency Anemia

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Additional information is available at the end of the chapter

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Abstract

Iron is an important element in living systems as it participates in a series of metabolic processes including DNA synthesis and oxygen and electron transport. Iron deficiency is the most common cause of anemia globally being an important healthcare problem. If left untreated, iron-deficiency anemia (IDA) can cause significant morbidity and often is the result of a more serious underlying condition. Correcting iron deficiency and replenishing iron reserves are important objectives of a well-conducted treatment, but diagnosis should prompt further investigation to establish the cause for potential reversal. Age, tolerance, preferred route of administration, and severity of anemia are some of the patient's characteristics which require an individualized approach.

Keywords: anemia, iron deficiency, hemoglobin, ferritin, transferrin, hepcidin, erythropoiesis

1. Introduction

Anemia is the most common hematologic disorder, iron deficiency being the leading cause worldwide [1]. Often, anemia is the presenting sign of a more serious underlying condition which left untreated can generate consequent morbidity [2]. Likewise, it can worsen preexisting comorbidities such as cardiac and pulmonary disease. The World Health Organization (WHO) defines anemia as hemoglobin levels lower than 13 g/dL in men and 12 g/dL in women (**Table 1**) with variations in age and pregnancy. Moreover, altitude and smoking status can influence baseline hemoglobin [3, 4]. Red blood cells (RBC) are responsible for hemoglobin levels. Deficits in their production, increased destruction, or loss through bleeding are the main three mechanisms by which anemia occurs. Risk factors include female gender, extremes of

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Population	Mild anemia	Moderate anemia	Severe anemia
Children 0.5–4 years	10–10.9	7–9.9	<7
Children 5–11 years	11–11.4	8–10.9	<8
Children 12–14 years	11–11.9	8–10.9	<8
Pregnant women	10–10.9	7–7.9	<7
Nonpregnant women	11–11.9	8–10.9	<8
Men >15 years	11–12.9	8–10.9	<8

Levels of Hb higher than the superior value of mild anemia in each population group are considered nonanemia.

Table 1. Severity of anemia in different age groups, sex, and pregnancy status (g/dL).

age, pregnancy, and lactation. There are several types of anemia such as thalassemia, sickle cell disease, aplastic anemia, hemolytic anemia, pernicious anemia, and iron-deficiency anemia. In this chapter we will focus on a comprehensive characterization of iron-deficiency anemia (IDA).

2. Definition

Iron deficiency and IDA are serious health problems in the whole world. Iron has a vital role for many biologic functions including energy production, respiration, and cell proliferation. IDA is the end-stage result of the lack of iron in the body resulting from inadequate iron intake, increased iron loss, or excessive iron requirements [5]. As a consequence, erythropoiesis is insufficient to fulfill the body's physiologic needs. IDA diminishes working performance by constraining muscles to depend on anaerobic metabolism in order to greater attain muscle extent in contrast to healthy individuals. As a result, in affected patients the capability to perform physical labor is decreased. Furthermore, in children, both growth and learning capacities are affected.

Using the severity criteria, anemia is classified into mild (11 g/dL to normal), moderate (8 g/dL to 11 g/L), and severe (less than 8 g/dL) in adult males and adult nonpregnant females (**Table 1**) [6]. Severe anemia may produce hypoxemia enhancing the occurrence of coronary insufficiency and myocardial ischemia. Also, it may aggravate underlying cardiac and pulmonary disorders.

3. Epidemiology

Anemia is a public health problem that affects populations in both developed and undeveloped countries. According to the WHO data on the prevalence of anemia for the period between the years 1993 and 2005, anemia affects 24.8% of the population globally, which corresponds to approximately one in four people. The highest prevalence was reported in preschool-aged children (47.4%), whereas the lowest prevalence is in men (12.7%). Although the prevalence in nonpregnant women was reported at 30.2%, they represent the population group with the largest number of individuals affected (468.4 million).

WHO region	Pregnant women	Nonpregnant women	Preschool-aged children
Africa	57.1	47.5	67.6
The Americas	24.1	17.8	29.3
Southeast Asia	48.2	45.7	65.5
Europe	25.1	19.0	21.7
Eastern Mediterranean	44.2	32.4	46.7
Western Pacific	30.7	21.5	23.1
Global	**41.8**	**30.2**	**47.4**

Table 2. Prevalence of anemia in different WHO regions (in percentage (%)).

Typically, IDA represents approximately a half of all types of anemia, but the cases may vary among population groups and in different areas according to local conditions [7].

The WHO areas of Africa and Southeast Asia have the highest risk, where about two-third of preschool-aged children and half of all women are affected [8]. Prevalence in pregnant and nonpregnant women is similar in Europe and the Americas, whereas preschool children's prevalence of anemia is different in these two WHO regions (**Table 2**).

4. Etiology

The diagnosis of IDA is not sufficient; the cause of iron deficiency has to be identified. Iron deficiency occurs by disturbing the balance of iron metabolism, respectively, by **reducing the intake** or by excess **blood loss** [9].

The main situations responsible for reduced iron intake, directly or indirectly, are insufficient food intake, poor absorption, or increased requirements [10].

Regarding the insufficient food intake, this situation is rarely encountered as iron requirements are relatively low. It is more common in severe diets and vegetarianism, as heme iron, the one contained in red meat, has two times greater bioavailability than the non-heme iron from eggs and vegetables [11].

Several conditions may interfere with iron absorption, the most frequent being:

- *Achlorhydria*: prevents the absorption of nonheme iron [12].
- *Gastrectomy*: absence of gastric acidity and reduction of food contact time with digestive lining [11].
- *Long-lasting antacid treatments* reduce iron absorption [11].
- *Eating habits*: excessive consumption of tea and coffee [13].
- *Gastritis with Helicobacter pylori* [14].
- *Inflammatory diseases of the small intestin*e: Crohn's disease, Whipple's disease, and celiac disease [11].

Some physiological conditions are associated with increased needs of iron and secondary apparition of IDA. Pregnancy, prematurity, twins, intense growth, and development periods during adolescence could be responsible of IDA [15–17].

The most common cause of iron deficiency remains blood loss, especially from the digestive track in men and from menstrual bleeding in women [18]:

- *Digestive conditions* may be caused by hiatal hernia, atrophic gastritis, gastric and duodenal ulcers, digestive cancers, colonic polyps, ulcerative colitis, and hemorrhoids [19–22].
- *Respiratory conditions* as lung cancers [23] or chronic infection and tuberculosis [23–24].
- *Genitourinary conditions as* menometrorrhagia, benign uterine tumors or malignant conditions, and hematuria [25–28].

Other conditions, more rarely observed, are frequent phlebotomies in blood donors, chronic kidney disease, and dialysis [29, 30].

5. Physiopathology

5.1. General aspects

IDA occurs through the disruption of iron metabolism. For a better understanding of the mechanisms by which iron balance can be altered, some important elements of iron metabolism must be taken into consideration:

1. The iron intake compensates only the physiological losses that occur through gastrointestinal epithelium exfoliation and urinary excretion [31].
2. In case of high demand or iron overload, the only regulation mechanism is represented by the digestive absorption which can be intensified or reduced. The regulation mechanism is not realized by increasing the physiological losses [32].
3. The total body iron accounts for 3–4 g in adults, and it is distributed in three compartments [33]:
   a. The functional compartment from which 70% of the total iron (2.8 g) consists in iron from hemoglobin and myoglobin and < 1% in cellular enzymes involved in oxidative metabolism: catalases, cytochromes, and myeloperoxidases.
   b. Transport compartment which represents 0.1% of the total iron, 4 mg, consists of transferrin or siderophilin. It is synthesized by the liver and has the role of transporting iron to cells. Each molecule fixes one or two atoms of trivalent iron. The evaluation of this compartment is made by:
      - Measurement of serum transferrin using immunological method.
      - Measurement of total iron-binding capacity.
      - Measurement of transferrin saturation
   c. The storage compartment represents 29% of total iron (1 g) and is contained in macrophages and hepatocytes under the form of:

- Ferritin, a water-soluble protein formed from apoferritin and iron, is found in the intracellular compartment, especially in macrophages. As the circulating iron increases, the ferritin levels also increase. A small amount is found in the blood, can be dosed, and correlates with body iron deposits.
- Hemosiderin represents a partially denatured form of ferritin. Hemosiderin found in macrophages (most of them are available by sternal bone marrow aspiration) can be identified after staining with potassium ferrocyanide (Perls staining) [34, 35].

5.2. The iron cycle

A balanced diet accounts for 10–20 mg of iron per day, of which 5% is absorbed, sufficient for covering the losses [31]. To provide the stores with the sufficient amount of iron, approximately 1 g is necessary, equivalent to the absorbed quantity in 2–3 years.

The iron intake consists of two forms [11]:

- Heme iron in red meat, more easily absorbed, in which iron exists as Fe^{2+}.
- Non-heme iron from eggs and vegetal products which is in the form of Fe^{3+}.

Iron absorption is impaired by antacids, phytates, and tannic acid. It takes place mostly in the duodenum and proximal intestine. Under conditions of rapid intestinal transit, the contact time of intestinal content with iron is reduced, and absorption is diminished. Trivalent iron is reduced to ferrous iron by the other food components or by reductase enzymes in intestinal brush cells [11, 36].

Ferrous iron is transported from the apical pole of the cell to the basal pole by the transport protein, divalent metal transporter 1 (DMT1). From this point, it is transported into the blood by ferroportin, as ferrous iron. Ferroportin's activity is regulated by hepcidin, an acute-phase protein synthesized by the liver. Hepcidin inhibits intestinal absorption of iron by accelerating degradation of ferroportin. The iron is then taken up by the transferrin. The iron-transferrin complex circulates in the blood until it interacts with specific receptors for transferrin. The complex coupled with transferrin receptors is internalized, and the iron is released and used for the synthesis of heme, while the transferrin-receptor complex reaches the cell surface where transferrin is released in the blood. At this point, a small amount of transferrin receptors can be released in the blood and can be dosed as free circulating receptors [9, 11].

In erythroid precursors, excess iron binds to apoferritin to form ferritin. This process also takes place in other cells that express transferrin receptors, for example, hepatocytes. Hepcidin inhibits iron release from macrophages. Iron incorporated in hemoglobin enters the circulation providing oxygen to tissues [37, 38].

The lifespan of a RBC is 120 days [33]. Then, erythrocytes are recognized as senescent cells by the reticuloendothelial system (RES) and hepatocytes, and as a result, they are destroyed by the phagocytes [39]. Hemoglobin is decomposed to globin and restores the deposit of amino acids. The iron is transported to the cell surface where it is taken by transferrin (iron recycling) [40].

The absorption is controlled by an active mechanism. It is influenced by several factors. RBC hyperplasia stimulates the absorption of iron, even if iron storages are normal or increased

and hepcidin levels are reduced. The molecular mechanism behind is unknown. Patients with associated anemia and ineffective erythropoiesis (thalassemia intermedia) have an excessive absorption of iron. In IDA, the hepcidin level is low, and iron is more efficiently absorbed from food. During inflammation, hepcidin levels increase, due to the fact that it is an acute-phase protein. This determines macrophages to retain the iron and to reduce iron absorption, determining iron deficiency [33, 41, 42].

Ferroportin acts also on the erythrocyte precursors, promoting the export of the iron to RBC precursors (**Figure 1**) [43].

5.3. Stages of iron deficiency

The first stage of iron deficiency is the reduction of iron stores. In order to compensate the deficiency, the iron is released from the stores, initially from ferritin, which is easily available, and then from hemosiderin. Thus, iron intestinal absorption and transferrin synthesis intensify, but on the other hand, the iron saturation of transferrin is reduced, and total binding capacity of transferrin increases. At this stage, due to the mobilization of iron from the stores, the levels of circulating iron are normal [44].

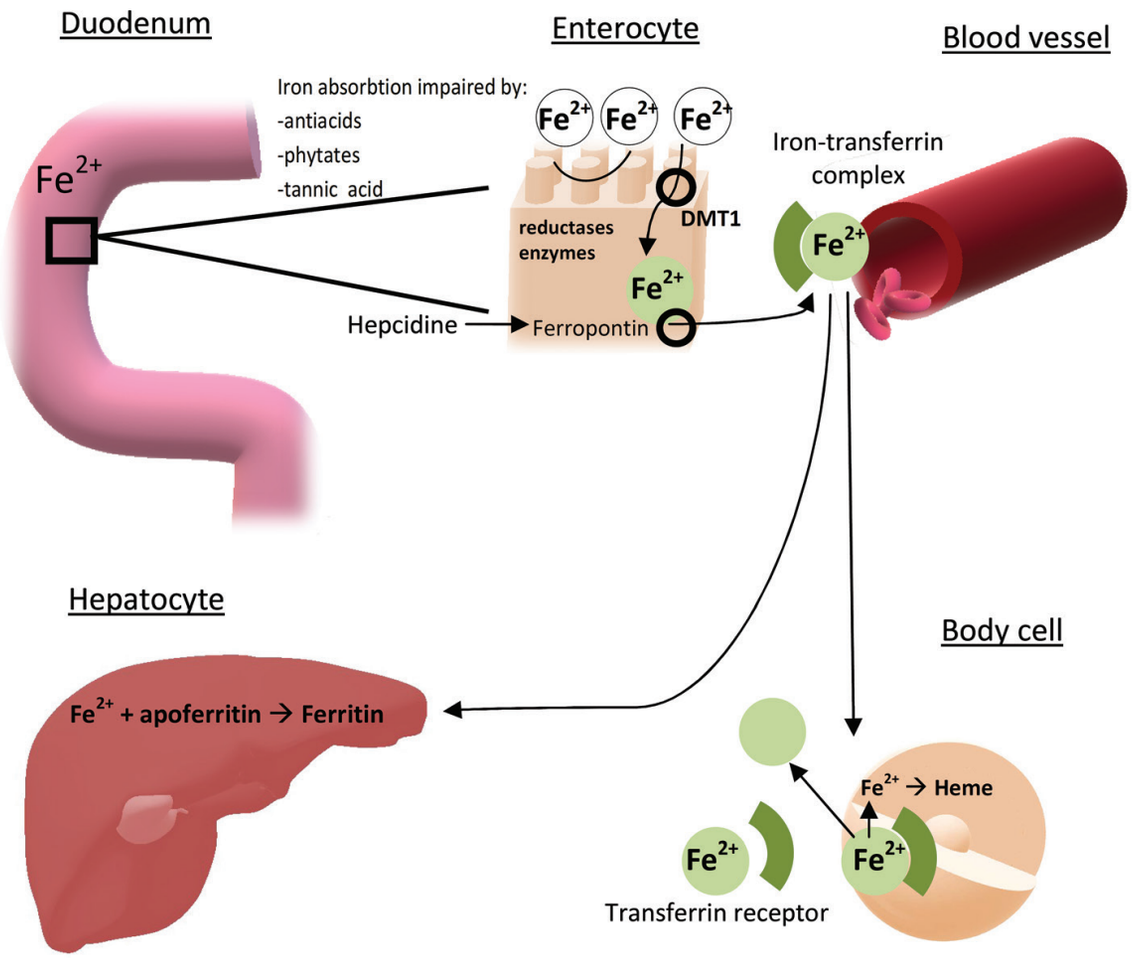


Figure 1. Schematic representation of iron circuit in the human body.

The second stage is represented by the total depletion of iron stores. At this moment the serum iron is low, but erythropoiesis is not affected [44].

The last stage is represented by the hypochromic microcytic anemia. At this stage, the quantity of iron delivered to the erythroblasts is insufficient, the synthesis of hemoglobin is reduced, and hypochromia occurs. Afterward, by enhancing the mitotic erythroblast activity, microcytosis occurs. The number of RBC is diminished, but not lower than the amount of hemoglobin. Due to the hypoxia, erythropoietin synthesis is stimulated, but the erythropoiesis cannot increase because of the low amounts of hemoglobin. Therefore, reticulocyte count will be normal or decreased. Iron deficiency causes the reduction of other body components that contain iron, such as myoglobin, cytochromes, and catalases, which are responsible for the late extrahematologic signs of iron deficiency [44, 45].

6. Clinical presentation

The clinical features of IDA depend on many factors including age group, comorbidity, anemia level, and speed of onset. Several symptoms may be present, some associated with all types of anemia such as pallor or asthenia. Other symptoms are caused by the iron deficiency that affects the epithelial cells, or in some cases, the symptoms may be caused by the disease which determined the disruption of iron metabolism.

Symptoms and signs resulting from anemia depend on the underlying cardiovascular status of the patient, most important being summarized in **Table 3**.

Depending on the underlying condition that caused the iron deficiency, the patients may present different symptoms and signs such as abdominal pain, urinary and genital symptoms, and respiratory disorders. The most frequent conditions associated with iron deficiency are gastric and duodenal ulcers; hiatal hernia; digestive carcinomas; and surgical interventions such as gastrectomy, intestinal resections, or urogenital pathology, for example, uterine fibroid, genital cancer in women, and kidney diseases that cause hematuria [46–48].

Symptoms caused by tissue hypoxia	**Symptoms caused by the heart or lung adaption to hypoxia**	**Symptoms and signs due to iron deficiency**
• Pallor	• Tachycardia	• Dysphagia
• Fatigue	• Tachypnea	• Plummer-Vinson syndrome
• General weakness	• Dyspnea	• Nail changes, koilonychia
• Headache		• Friable hair
• Vertigo		• Angular cheilitis
• Tinnitus		• Stomatitis
• Angina pectoris		
• Intermittent claudication		
• Poor appetite		

Table 3. Symptoms associated with iron deficiency.

7. Diagnosis of IDA

Diagnosis of IDA involves reduced hemoglobin levels and disturbed iron parameters. The initial evaluation includes a complete blood count (CBC), reticulocyte count, peripheral blood smear, and serum iron parameters. The CBC is useful in determining the concentration of hemoglobin, the mean corpuscular volume, and the average size of RBC.

The CBC highlights:

- Low hemoglobin level.
- The number of RBC decreases later but proportionally less than the hemoglobin levels.
- The mean corpuscular volume (MCV) is <80 fl and HEM <27 pg.%. So, anemia is a hypochromic microcytic because of the decreased hemoglobin level.
- Reticulocyte count is normal or slightly elevated.
- On the blood smear, erythrocytes have a fading center with a periphery of hemoglobin (anulocytes).

RBC dimensions are variable, unequal in size and generally smaller, this situation being known as anisocytosis. This reflects an increased red blood cell distribution width index (RDW). The number of white blood cells and their morphology is normal, whereas moderate thrombocytosis is frequently encountered, but it resolves after the correction of iron deficiency.

After the diagnosis of anemia, one should proceed to explore the iron metabolism. Evaluation of serum ferritin is the most used diagnostic test, but its level increases in inflammatory disease and in old persons. For the diagnosis of IDA, some parameters as transferrin, soluble transferrin receptor (sTfR), and the soluble transferrin receptor/ferritin index could be useful. The accuracy of some of these markers is limited being influenced by many other conditions, especially the level of serum ferritin. The most used parameter, serum ferritin level, can be increased in acute or chronic inflammation, old persons, chronic infection, or malignancy status. One more sensitive parameter for IDA diagnosis is soluble transferrin receptor (sTfR) that remains unaffected by inflammatory states being an indirect measure of erythropoiesis.

Usually, in clinical practice, the diagnosis of IDA includes low hemoglobin level, low transferrin saturation (<15%), low levels of serum ferritin (<30 ug/dl), and high total iron binding capacity (>13.1 umol/l). Another method of exploring iron reserves consists in the appreciation of the medullary reticulocytes through a medullary smear (bone marrow cytology) and Perls staining. This highlights the absence of hemosiderin (iron reserves), the absence of sideroblasts (lack of iron in erythroblasts), and the absence of siderocytes (lack of iron in red blood cells). This exam is not routinely required.

Finally, after establishing the diagnosis of IDA, an iron deficiency cause should be investigated, as the most common cause in men is digestive losses and in women genital losses. These investigations should include gynecological examination and the exploration of the digestive tract: gastroscopy, colonoscopy, and other investigations according to specific elements identified in the medical history and physical exam [33, 49–51].

8. Differential diagnosis

The differential diagnosis of IDA should be made with other forms of microcytic anemia (see **Table 4**):

(a) Anemia from chronic disease where one of the main mechanisms is the blockage of iron in its reserves, as in macrophages and the inability to be used in erythropoiesis.

Common elements:

- Hypochromic microcytic anemia.
- Serum iron is low.

Elements of differential diagnosis:

- The total capacity of iron attachment is normal or decreased (overall amounts of iron are not decreased).
- Ferritin is normal or increased (acute-phase protein, iron reserves are increased).
- Signs of the underlying disease are present: chronic infections, collagen diseases, neoplasia, etc.
- Biological markers of inflammation are present: fibrinogen, C-reactive protein, alpha-2-globulin, etc.)

(b) Thalassemia minor

Common elements:

- Hypochromic microcytic anemia.

Elements of differential diagnosis:

- The number of RBC is twofold higher.
- The RDW (erythrocyte distribution index) is normal.

Anemia from chronic disease
Chronic inflammatory disorders
Chronic infections
Autoimmune diseases
Kidney diseases
Cancer
Thalassemia minor
Sideroblastic anemia

Table 4. Differential diagnosis of iron-deficiency anemia.

Smear shows frequent red blood cells with basophile points and bull's-eye erythrocytes (codocytes):

- Serum iron is normal.
- Ferritin is normal or increased.

The diagnosis of certainty is determined by hemoglobin electrophoresis: increased amount of fetal hemoglobin (HbF) or hemoglobin A2.

(c) Sideroblastic anemia

Common elements:

- Hypochromic microcytic anemia.

Elements of differential diagnosis:

- Normal or increased serum iron.
- Increased level of ferritin.
- There is no chronic disease or biological signs of inflammation.
- Bone marrow cytology with Perls staining: ring-shaped sideroblasts (the iron is placed in the mitochondria with a ring around its core).

Difficulties in diagnosis:

- Previous treatment with iron supplements.
- Association with other deficits.
- Association with an anemia from chronic diseases [52–54].

9. Treatment

9.1. General aspects

Iron-deficiency anemia and/or iron deficiency should be treated, regardless of the presence or absence of symptoms. The correction of anemia is vital; depending on its severity, anemia could trigger cardiovascular complications, sometimes severe [55, 56].

Treatment of IDA has two major objectives:

1. Substitution treatment with iron products, aiming to correct anemia and replenishing the iron reserves
2. The detection and treatment of the underlying cause of anemia

9.2. Iron therapy

The treatment of iron deficiency is either enteral or parenteral.

Intramuscular administration of iron is rarely used due to local complications such as pain at administration site, uneven absorption, skin pigmentation, and even development of sarcomas at the injection site as some authors have reported [57, 58].

Transdermal administration has been experimented in animal models, but there is no evidence that it would be effective and safe in humans [59].

9.2.1. Oral iron therapy

9.2.1.1. Treatment with oral iron products

Treatment with oral iron products is preferable due to the low cost and lack of anaphylactic side effect. Usually, it is used to treat iron-deficiency anemia in children and adolescents.

Indication:

The main indications of oral iron are treatment of IDA, treatment of iron deficiency, and prophylaxis of iron deficiency in subjects with high needs such as pregnant women, adolescents, and preterm children.

A wide range of iron products is available in forms of tablets or liquid. Liquid iron products have the advantage of allowing titration of the dose. The most commonly used oral iron products are polysaccharide iron complex, ferrous gluconate, ferrous sulfate, and ferrous fumarate.

Dosage:

Regarding the dosage, various over-the-counter tablets exist depending on the products, but generally, there are no differences between these products in effectiveness or adverse events. The daily dose needed to correct iron deficiency depends on age, iron deficiency, and urgency. In general, daily dose for the correction of IDA with oral products is 150–200 mg elemental iron. Reports show that this dose taken every other day is most effective and has a better absorption and fewer side effects [60, 61].

Toxicity of iron products is more important in elderly patients, so doses are smaller. In a randomized study of 90 patients, of over 80 years old with iron deficiency, doses of 10, 15, or 150 mg for 2 months were equally effective [62].

The bioavailability and absorption of oral iron products may be influenced by food (e.g., phytates, phosphates, and tannins can bind iron and prevent absorption) or by drugs which diminish gastric secretion (antacids, histamine receptor inhibitors, proton pump inhibitors, etc.) reducing the absorption of iron. This is why iron products are administered 2 hours before and 4 hours after the administration of antacid absorption of iron as ferrous iron depending on acidic environment.

In general, iron product administration is associated with acidic foods (orange juice) or vitamin C to promote iron absorption, but there are no studies that show a positive effect of vitamin C in the absorption of iron [63].

There is no consensus on the duration of treatment with oral iron products. Some experts end treatment after correcting anemia to allow early detection of secondary anemia, due to recurrent blood loss. Others recommend continuing treatment for 6 months after correction of anemia in order to supplement iron reserves. Generally, 6 weeks of treatment are needed to correct anemia, followed by 6 months to replenish the reserves.

Side effect of oral therapy:

Concerning the side effects of oral iron therapy, the most common side effects involving gastrointestinal tract are metallic taste, nausea, flatulence, constipation, diarrhea, epigastric pain, and/or vomit. Black stools create anxiety as they may be misinterpreted as gastrointestinal bleeding.

Some measures can be taken in order to diminish iron side effects and increase tolerability as increasing the time between administrations (given every other day, not daily), changing diet (concomitant administration of food, even if absorption is reduced), reducing daily dose of elemental iron, switching from tablets to liquid preparations that allow titration of doses, or switching from tables to IV administration.

9.2.1.2. Treatment with IV iron products

Indication:

There are some specific indications for IV administered iron products when oral administration is inefficient or contraindicated (see **Table 5**):

- Patients who do not tolerate oral products due to gastrointestinal symptoms especially elderly, pregnant women, and patients with gastrointestinal disorders for which the administration of these products may aggravate symptoms.
- Patients with uncontrollable chronic blood loss that cannot be corrected by oral treatment (Rendu-Osler disease and other vascular malformations, cancer, etc.).
- Patients who have undergone surgery of the digestive tract that affects the absorption: gastrectomies and surgical bypass.
- Patients with pathology associating malabsorption or inflammatory disease like celiac disease, Whipple disease, etc.
- Patients who require replenishing iron reserves in one to two sessions instead of prolonged treatments.

Oral therapy	Parenteral administration
Indication	**Indication**
• Treatment of iron deficiency and prophylaxis of iron deficiency in subjects with high needs such as pregnant women, adolescents, and children	• Intolerance or conditions associated with malabsorption of oral products • Uncontrollable chronic blood loss • Patients who require replenishing iron reserves in one to two sessions instead of prolonged treatments
Side effects	**Side effects**
Gastrointestinal disorders: • Nausea • Flatulence • Constipation • Diarrhea • Epigastric pain • Vomit	• Allergic reactions as anaphylactic shock or located rash • Heart palpitations • Dizziness • Muscle spasms of the neck and scapula-vertebral region • Risk of infection

Table 5. Iron therapy: Indication and side effects of enteral versus parenteral administration.

Administration of IV products leads to reduced transfusion requirements for certain patients reducing the risk of posttransfusion adverse reactions.

Several iron products are available for IV administration; the most important are ferric carboxymaltose (FCM), ferric gluconate (FG), ferumoxytol, iron sucrose (IS), iron isomaltoside, and low molecular weight iron dextran (LMW ID).

Differences between these products consist in cost and the number of visits required for the administration of the total dose, namely, the time of administration and the number of doses required.

The total amount of iron required depends on the intended purpose, correcting anemia or supplementing the iron reserves.

Dose calculation is based on body weight, patient hemoglobin levels, and elemental iron/ml concentration of the product. In clinical practice, a 1000 mg dose of iron is generally enough to treat anemia. Generally, no premedication prior to IV administration is needed, except for patients with a history of asthma or drug allergies or patients with inflammatory arthritis for which 125 mg of methylprednisolone before iron administration is recommended [64].

Generally, antihistamines are not used in preventing side effects [65–67].

Administration and dosing of various iron products:

LMW Fe Dextran: It can be given in a single dose of 1000 mg in 250 ml of saline, 1 hour infusion, or multiple doses of 2 ml, i.e., 100 mg elemental Fe (2 ml ampoule, 50 mg Fe/ml).

If single dose is preferred, a test dose of 0.5 ml is administered in 30 seconds prior to the infusion.

Ferric gluconate (Ferrlecit): It is administered in a 10–15 ml dose, the equivalent of 125–187.5 mg (1 ampoule contains 12.5 mg of elemental Fe/ml). In patients with drug allergies, it is recommended to administer a test dose prior to infusion. Each dose can be given by bolus or infusion of 20–30 minutes.

Fe sucrose (Venofer): Multiple infusions with a maximum dose of 10–15 ml, equivalent to 200–300 mg of elemental Fe (ampoule 20 mg/ml), are administered. It is recommended to administer a 1.25 ml test dose (25 mg IV, administered slowly to patients with drug allergies).

Ferumoxytol: It consists of superparamagnetic iron oxide nanoparticles coated with a low molecular weight semisynthetic carbohydrate. It is administered at a dose of 17 ml, the equivalent of 510 mg elemental Fe (ampoule 30 mg/ml), with a 15 minute infusion.

Ferumoxytol may interfere with magnetic resonance imagery (MRI), which can lead to errors in interpreting the results.

Ferric carboxymaltose (Ferinject): It is used in 20 ml dose, equivalent to 1000 mg of elemental iron (the vial contains 50 mg/ml, the maximum dose being 20 mg Fe/kg body weight).

Doses are given in a 15 minute infusion. It is efficient and safe [68–71]. It can sometimes cause hypophosphatemia.

Iron isomaltoside (Monofer): It has a matrix structure where lean iron is slowly removed, allowing administration of 20 mg/kg infusion at 15 minutes; the ampoule is 100 mg/ml. It does not require a test dose. Efficacy has been demonstrated in inflammatory bowel disease, chronic renal disease, heart surgery, and chemotherapy-induced anemia [72–76].

Side effects of IV iron products:

The most common side effects consist in allergic reactions, sometimes anaphylactic shock. However, these reactions are extremely rare and often overestimated.

Patients with inflammatory arthritis (rheumatoid arthritis) may experience an exacerbation of symptoms during iron infusion, which can be prevented by administering 125 mg of methylprednisolone.

Reducing the risk of allergic reactions can be achieved through the following measures:

- Avoidance of administration of parenteral iron products to patients known for hypersensitivity reactions in the past.
- Non-premedicating patients without asthma or allergic reactions.
- Preventing the exacerbation of the symptoms of inflammatory arthritis patients by administering methylprednisolone.
- Stopping the infusion if symptoms occur.

Nonallergic reactions may occur, which include located rash, heart palpitations, dizziness, muscle spasms of the neck, scapula-vertebral region, etc.

The risk of infection may be increased because iron acts as a growth factor for bacteria. This is supported by some authors but denied by others [77, 78].

9.3. Monitoring and evaluating response to treatment

Monitoring the response to iron therapy depends on the severity of anemia and on the way of iron administration. For patients treated with oral products, reassessment is done after 2 weeks of treatment by checking Hb levels and reticulocytes. For parenteral treatment, reevaluation is done after 4–8 weeks. Iron treatment is continued until ferritin and transferrin return to normal. There are some either clinical or laboratory criteria used to monitor the efficacy of treatment with iron.

Amelioration of asthenia and installation of a well-being state in the first days of treatment besides the increased level of hemoglobin within 1–2 weeks of treatment seem to be the most important parameters related to iron-deficiency correction. In patients with severe anemia, a modest reticulocytic crisis occurs within 7–10 days after the initiation of treatment. In those with mild anemia, this reticulocytosis is not encountered.

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10. Evolution and prognosis

After iron treatment, erythropoiesis with reticulocytosis efficiency occurs after 1–2 weeks of treatment, followed by an increase in hemoglobin levels. This increase (the so-called reticulocyte crisis) is not as expressed as in vitamin B12 or folic acid anemia treatment in megaloblastic anemia. With treatment, anemia is corrected in about 1–2 months, but for replenishing the iron reserves, it is necessary to continue for about 4–6 months of treatment.

Prognosis of patients with IDA depends mainly on the underlying condition that caused iron deficiency and on the cardiovascular status of patients.

Failure to respond to treatment with iron may occur in several circumstances, the more frequent observed being:

- Reduced patient compliance and treatment interruptions.
- Some conditions responsible for malabsorption in case of oral iron products.
- Excessive bleeding where oral products cannot compensate for blood loss
- Association of more types of anemia.
- Association with inflammatory disease blocking iron balance regulation.

Celiac disease and *Helicobacter pylori* infection may reduce the absorption of iron, thus being a frequent cause of failure to oral iron treatment.

An important part of fighting iron-deficiency anemia is treating its underlying cause.

Red blood cell transfusion is not generally required in iron-deficiency anemia, but in severe cases such as symptomatic patients associating cardiac pathology, transfusion is required in order to ameliorate symptoms until iron deficits are corrected.

11. Conclusion

Multiple factors can contribute to iron imbalance in the human organism. Reduced absorption, increased losses, and/or increased requirements are the main mechanisms resulting in iron deficiency. Often such factors can coexist requiring a complex management of the consequent anemia. Iron therapy should be individualized by patient's characteristics. Treatment of underlying conditions is an important step toward reducing iron-deficiency-anemia-associated morbidity.

Conflict of interest

All authors have read and approved this version of the book chapter, and due care has been taken to ensure the integrity of the work. No part of this work has been published or submitted elsewhere. No financial conflict of interest exists in the submission of this manuscript.

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