Iron Deficiency and Iron Deficiency Anemia in Children

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Additional information is available at the end of the chapter

Abstract

Iron deficiency anemia is considered the most common and widespread nutritional form of anemia in childhood. Red cells are hypochromic and microcytic with low mean corpuscular volume (MCV), low mean corpuscular hemoglobin (MCH) and low reticulocyte hemoglobin content (CHr). Red blood cell distribution width (RDW) is increased. Serum iron is reduced, transferrin is increased and serum ferritin is decreased. Prematurity, decreased dietary source, malabsorption and blood loss represent the most common causes of iron deficiency. Recommended oral dose of elemental iron is 2–6 mg/kg/day; when normal hemoglobin values are reached, treatment must be generally continued for 3 months in order to replenish iron stores. Rarely intravenous therapy is required. The pediatricians and other health care providers should strive to prevent and eliminate iron deficiency and iron-deficiency anemia.

Keywords: iron deficiency, anemia, children, hypochromic microcytic anemia, prevention

1. Introduction

In children, iron represents an essential nutrient for growth and proper function of many organs and systems, mainly erythropoiesis. It must be obtained from the diet and absorbed in the upper gastrointestinal tract. When iron requirements are not met, as when the balance of iron intake, iron stores and the body's loss are insufficient to fully support the production of erythrocytes, it is referred to as iron deficiency (ID). In 30% of cases, the ID, if left untreated, evolves in iron deficiency anemia (IDA) which represents the most frequent form of anemia in childhood.

2. Epidemiology

ID and IDA are among the most widespread morbid conditions in the world and represent a public health problem both in developed and developing countries. All reports agree that IDA is the most common anemia worldwide in school-age children. A recent WHO report, obtained from 200 countries, showed a significant reduction in prevalence of ID/IDA that rose from 40.2% in 1990 to 32.9% in 2010. In countries with limited resources, ID affects about two-thirds of children and adolescents; it is estimated that around 25% of preschool children suffers from IDA. In Africa, the prevalence of IDA among school-age children still ranges from 64.3 to 71%. In Europe, the overall prevalence of ID/IDA is 2–4%, with two peaks between the first and third year of life (2.3–15%) and adolescence (3.5–13% in males, 11–33% in females). ID/IDA is less than 5% in Northern and Western Europe, but it is considerably higher in Eastern Europe (9–50%). In the United States, IDA prevalence is 1.6–7.4% among pediatric population; in children 1–5 years old, the prevalence of ID is 7–8% and about one-third of them have IDA. The prevalence is higher among children 1–2 years old (13.5 and 2.7%, respectively). Although the prevalence of IDA has decreased over the past decade, data from many surveys indicate that it remains relatively high among low-income family; the prevalence of ID/IDA was 17% in 1–2 years old and 6% in 3–4 years old among Mexican American toddlers, and 12% in 1–2 years old and 5% in 3–4 years old in other low-income family [1–7].

3. Pathophysiology

The amount of iron contained in the body, in relation to the various ages, is summarized in **Table 1**. During the first year of life, total-body iron increases by 240 mg; nearly 80% of that iron is used for expanded hemoglobin production (50%) and iron stores (30%). Over this age, iron intake or stores must remain sufficient for the ongoing growth and increased red cell mass. Iron metabolism is essentially a "closed system" in which almost all metal from the hemocateresis (about 95%) is continuously recycled to meet the demands of the various compartments, especially the production of new red blood cells (RBC). Only a small part of the body iron is represented by that absorbed from the diet. In adults, less than 5% of the iron requirement for the erythropoiesis is obtained from food while in the child the iron destined for hemoglobin synthesis derives for 30% from the diet; the remainder part come from the deposits and the rework of the iron released by the hemocateresis. From the sixth month, the total body iron progressively increases (70%) to answer to the high rate

	Newborn (3.300 kg)	Children (35 kg)	Adult (75 kg)
Total content	240–250 mg	1.5–2 g	2.5 (f)–4 (m) g
Hemoglobin	132–137.5 mg (55%)	1–1.4 g (68%)	2.00–2.72 g (50–70%)
Ferritin and hemosiderin (deposit)	101–105 mg (42%)	400–500 mg (27%)	0.81–1.08 g (15–30%)
Myoglobin		60–80 mg (4%)	120–300 mg (3–5%)
Enzymes	7–7.5 mg (3%)	9.12 mg (0.6%)	18–24 mg (0.2–5%)

Table 1. Iron content in the body in newborn, child and adult.

of growth and the expansion of the erythrocyte mass. As more than 60% of the iron absorbed is destined to this function (1 kg of weight corresponds to 75 ml of blood or 9 g of hemoglobin and 30 mg of iron). It is clear that in this age, iron balance is more precarious, and possible dietary imbalances could reduce tolerance limits (delayed weaning, vegetarian diet and malabsorption).

Physiological losses are minimal (about 0.5–1 mg/day) and are mostly due to exfoliation of the mucous membranes (bile, intestine, kidneys and lungs) and of the skin. Since there are no specific mechanisms of iron excretion through the liver or kidneys, iron balance is mainly controlled at the intestinal level by modulating its absorption. A balanced diet of an adult contains about 10–15 mg of iron. The absorption of iron in the foods, which varies from 5 to 15% (up to 20% for the meal), compensates the physiological losses. In case of blood losses (menstruation or other bleeding), acute or chronic hemolytic events, or periods of increased demand, such as rapid growth, pregnancy and competitive sports activity, intestinal absorption can increase up to four times.

Regarding the developmental age, the iron requirement (LARN 2014) to be taken with the diet, after 6 months is about 7–11 mg/day which corresponds to about 0.8–1 mg of iron absorbed. Of these, around 75% are used for growth and 25% to offset the losses. In adolescent age, after the appearance of the menarche (considering that with each menstrual cycle are lost about 10–25 mg of iron), the amount to be taken with the diet rises to 13–18 mg/day [6–15].

4. Etiology

The causes of iron deficiency are numerous, but in the children, these are basically due to four causes: decreased reserves at birth, inadequate intake with the diet, reduced intestinal absorption or chronic losses of blood. **Table 2** examines all causes [1–4]. "Physiological anemia"

Decreased reserves at birth: prematurity and/or twinning, intrauterine fetus-fetal and fetus-maternal transfusions, exanguino-transfusion at birth or severe IDA in the mother, early clamping of the umbilical cord.

Inadequate intake: late weaning, incongruous diet (uncontrolled vegetarian-vegan) and/or increased needs: rapid weight-growth such as low birth weight, prematurity, adolescent development and cyanotic heart disease.

Reduced absorption: celiac disease, intestinal bowel disease, Hirschsprung disease, large intestinal resections (short bowel), use of antacids and proton pump inhibitors, excess in the diet of phytates (soy and cereals), bran, starch, calcium, polyphenols (tea and coffee), soy protein, casein and egg white, *Helicobacter pylori* infection, giardiasis and other intestinal parasites, obesity, bariatric surgery, immune deficiencies with mucosal atrophy, intestinal lymphangiectasia.

Blood loss: abundant and/or frequent menstruation, intolerance of cow's milk protein, consumption more than 500 ml/day of cow-milk, Meckel's diverticulum, esophageal varices, polyps and hemorrhoids, intestinal bowel disease, intestinal parasitosis, epistaxis, severe hematuria, prolonged use of aspirin, cortisones, nonsteroidal anti-inflammatory drugs, frequent blood sampling for diagnostic purposes (in the newborn, especially if immature, and in the small infant).

Hereditary forms (rare diseases): DMT1 deficiency, transferrin deficiency, refractory iron deficiency anemia (IRIDA).

Chronic pulmonary diseases: pulmonary hemosiderosis, cystic fibrosis, bronchopulmonary dysplasia.

Iron deficiency anemia associated with anemia of chronic diseases.

Table 2. Main causes of iron deficiency in childhood and adolescence.

develops in the postnatal period, and iron stores are sufficient to provide erythropoiesis in the first 6 months of life if there is no significant blood loss. In low birth weight infants and in babies with perinatal blood loss, the stores are exhausted earlier. The amount of iron in breast milk is at the highest level in the first month, but it decreases gradually in the subsequent periods and is reduced up to 0.3 mg/l approximately in the fifth month. Although the amount of iron received from breast milk is typically low, its absorption is considerably high (50%). Solid foods, given after the sixth month, should be rich especially in iron, zinc, phosphorus, magnesium, calcium and vitamin B6. According to the WHO data, 98% of the iron requirement in infants aged 6–23 months should be introduced by solid foods. In patients, especially in older children and adolescents, blood losses should be considered, if inadequate intake can be excluded or there is inadequate response to iron treatment.

5. Clinical presentation

Mild iron deficiency, without anemia, mostly occurs asymptomatic or can only occur with poor exercise tolerance and/or asthenia. With the worsening of iron deficiency, asthenia becomes more relevant, especially in relation to the reduced amount of myoglobin and enzymes for the oxidative phosphorylation. When anemia appears, the most significant symptom is pallor of the mucous membranes and of the skin. In about 10% of children with IDA, there is modest splenomegaly as a result of mild hemolysis. The reduction in hemoglobin is slow. The child is
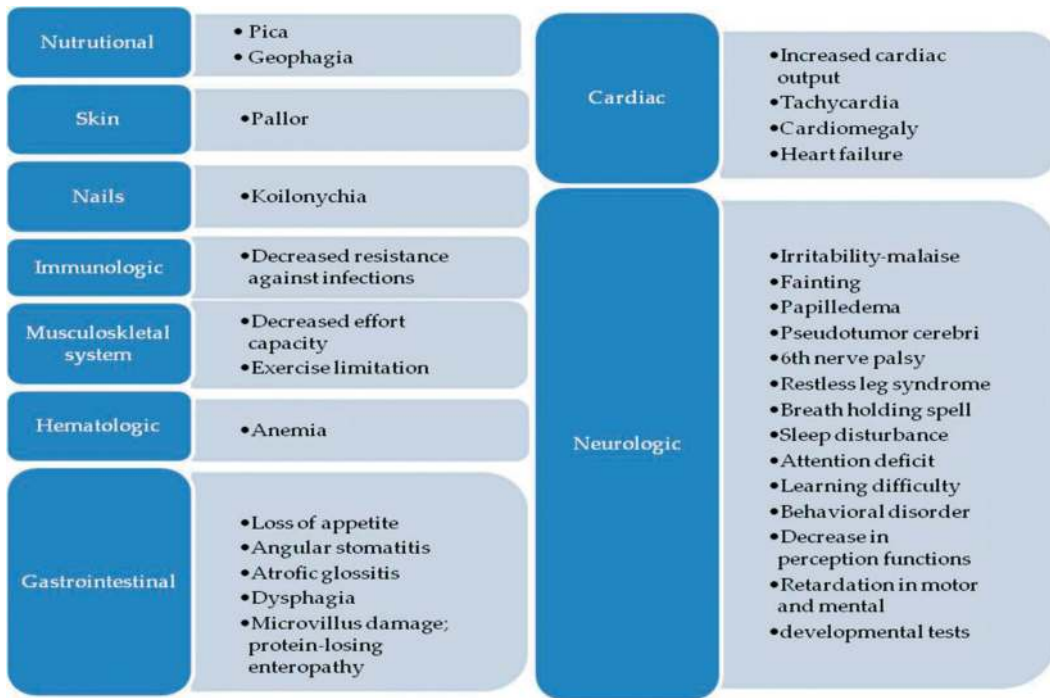

Figure 1. Manifestation and multisystem sequelae of iron deficiency.

able to compensate poor tissue oxygenation without significant clinical manifestations except for a modest tachycardia, with an increase in cardiac output and a moderate tachypnea. This mechanism is due to an increase of 2,3-diphosphoglycerate (2-3-DPG) in red blood cells, that induces a displacement to the right of the dissociation curve of the hemoglobin, allows a greater release of oxygen to the tissues.

Whereas iron plays a fundamental role in numerous metabolic processes in different organs and tissues, its deficiency is not only reflected on erythropoiesis but can also have consequences at various levels. The preschooler children may show lack of appetite, lack of desire to play and sometimes irritability; the older child can have asthenia, listlessness, headache and reduced school performance. Recent literature highlights the association between chronic iron deficiency and possible compromise of the central nervous system, with intellectual, attention, memory, learning, fine motor skills and verbal fluency deficits. Some studies have shown an association between iron deficiency and increased risk of developing stroke, idiopathic intracranial hypertension, cranial nerve paralysis, sleep disorders, febrile seizures and attention deficit and hyperactivity disorder (ADHD). Iron deficiency and chronic anemia can cause glossitis, angular cheilitis, dysphagia, reduction of gastric acidity, nail dystrophy, hair fragility, amenorrhea, slowing of growth and greater susceptibility to infections. In severe forms (hardly observable in our social context), we can observe pica (ingestion of nonnutritive substances) and/or geophagy (ingestion of earth or mud) [1–4, 7, 8, 14–20] (**Figure 1**).

6. Laboratory findings

Table 3 shows the normal values of the erythrocyte parameters in relation to age. In IDA hemoglobin, red blood cells and hematocrit are below two standard deviation (SD) respect normal value according to the age, gender and race. Typically, peripheral blood smear shows hypochromic (pale) and microcytic erythrocytes with variable size and shape (anisopoikilocytosis). Subtle change in morphologic features may be observed before than overt anemia occurs, as manifestation of iron-deficient erythropoiesis. Change of red cell distribution, evaluated by red cell distribution width (RDW) and hemoglobin distribution (HDS) usually are present before overt microcytosis (reduction of MCV) and hypochromia (reduction of MCH and MCHC) are observed. The values of the iron system parameters (serum iron, transferrin, total iron binding capacity and ferritin) undergo variations due to age and are summarized in **Table 4**. In ID/IDA, serum iron is reduced (less than 50 µg/dl), and serum transferrin is increased. Transferrin saturation index below 16% is considered very sensitive for IDA. Measurement of serum ferritin is currently the laboratory test recommended for diagnosing iron deficiency. In the absence of an associated disease, a low value is an early and highly specific indicator of ID. The WHO criteria proposed to define depleted iron storages are 12 µg/l for children under 5 years and 15 µg/l for those over 5 years. However, because ferritin is an acute-phase reactive protein, it may be elevated by infection, acute and chronic inflammatory disorders, malignant disease, liver disease and starvation. In particular, in case of infection or inflammation the cut-off for serum ferritin for diagnosis of IDA is elevated

Age	Hb (g/dl)		Ht (%)		GR (10^2/l)		MCV (fl)		MCH (pg)		MCHC (g/dl)	
	Mean	−2SD	Mean	−2SD	Mean	−2SD	Mean	−2SD	Mean	−2SD	Mean	−2SD
Bird	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30
1–3 days	18.5	14.5	56	45	5.3	4.0	108	95	34	31	33	29
1 week	17.5	13.5	54	42	5.1	3.9	107	88	34	28	33	28
2 weeks	16.5	12.5	51	39	4.9	3.6	105	86	34	28	33	28
1 month	14.0	10.0	43	31	4.2	3.0	104	85	34	28	33	29
2 months	11.5	9.0	35	28	3.8	2.7	96	77	30	26	33	29
3–6 months	11.5	9.5	35	29	3.8	3.1	91	74	30	25	33	30
0.5–2 years	12.0	10.5	36	33	4.5	3.7	78	70	27	23	33	30
2–6 years	12.5	11.5	37	34	4.6	3.9	81	75	27	24	34	31
6–12 years	13.5	11.5	40	35	4.6	4.0	86	77	29	25	34	31
2–18 years												
Female	14.0	12.0	41	36	4.6	4.1	90	78	30	25	34	31
Male	14.5	13.0	43	37	4.9	4.5	88	78	30	25	34	31
Adults												
Female	14.0	12.0	41	36	4.6	4.0	90	80	30	26	34	31
Male	15.5	13.5	47	41	5.2	4.5	90	80	30	26	34	31

Table 3. Normal erythrocyte parameters in developmental age.

to 30–50 μg/l. Combining the evaluation of the levels of c-reactive protein (CRP) is required to rule out an inflammation. In children, serum soluble transferrin receptor (sTfR) has been reported to be a sensitive indicator of iron deficiency and is appeared to be relatively less influenced by inflammation than ferritin. Unfortunately, reference values of these parameters in children are not available and not all laboratories may perform it. So far, in routine practice, evaluation of sTfR is not needed for a diagnosis of IDA. Reticulocyte hemoglobin (CHr) is another parameter useful for the diagnosis of ID. Values less than 27.5 pg are considered very sensitive and specific for IDA (83 and 72%, respectively). Measurement of red blood cell pro-toporphyrin IX and zinc protoporphyrin (ZPP), that are increased in IDA, provides another parameter that may help in the diagnosis. The combination of red blood cell parameters with serum ferritin and transferrin saturation index still remains the common approach to investigate anemia for the diagnosis of IDA. Serum hepcidin is a promising novel biomarker for the diagnosis of iron disorders. It is decreased in ID, and its levels may become undetectable in severe cases of IDA. As this marker is influenced by inflammation, renal and liver function, these conditions should be assessed. In the future, when commercial test for measurement of urinary or serum hepcidin will be available, these parameters might be useful in differential diagnosis. Thrombocytosis (platelets count between 500,000 and 700,000 mcL) occurs frequently. In severe forms of IDA may be present a low grade of hemolysis due to the rigidity

Age	Male	Female
Ferritin	ng/ml	ng/ml
1–30 days	6–400	6–515
1–6 days	6–410	6–340
7–12 months	6–80	6–45
1–5 years	6–24	6–24
6–9 years	10–55	10–55
10–14 years	23–70	6–40
14–19 years	23–70	6–40
Serum iron	μg/dl	μg/dl
1–5 years	22–136	22–136
6–9 years	39–136	39–136
10–14 years	28–134	45–145
14–19 years	34–162	28–184
TIBC	μg/dl	μg/dl
1–5 years	268–441	268–441
6–9 years	240–508	240–508
10–14 years	302–508	318–575
14–19 years	290–570	302–564
Transferrin	mg/dl	mg/dl
1–30 days	97–205	92–208
1–6 months	106–325	128–309
7–12 months	178–357	145–364
1–3 years	196–365	149–382
4–6 years	202–350	174–399
7–9 years	149–353	186–368
10–12 years	173–380	185–377
13–15 years	171–374	193–391
16–18 years	194–348	181–416

Table 4. Values of serum ferritin, serum iron, total iron binding capacity (TIBC) and transferrin in pediatric age (ranging from 2.5 to 97.5 percentiles).

of red cell membrane, than mild increase of hemolysis markers may be observed. Bone marrow examination is no longer performed in the work-up for IDA for assessing iron stores. However, as diagnosis of iron deficiency is somewhat complex, the use of several combined indicators seems to provide the best assessment of iron status.

Iron deficiency develops in three steps. The first one is iron depletion or prelatent stage. Iron stores are lowered or absent (serum ferritin is reduced below normal cut-off) while other parameters are unchanged. In this stage, erythropoiesis is still normal. The second stage is defined as latent stage or deficiency. Iron supply for erythropoiesis became reduced; serum iron transferrin saturation are reduced as well as CHr; StfRs increases. The third stage overt IDA is characterized by a progressive impairment of erythropoiesis and modifications of hematological parameters [1–4, 8, 9, 20–32].

At the end of this process appears the hypochromic microcytic anemia characterized by:

- Reduction of Hb, RBC number and hematocrit
- Reduction of MCV, MCH and MCHC
- Hypochromic cells with a tendency to microcytosis
- Increase of RDW > 15%
- Reduction of CHr <27.5 pg
- Reduction of serum iron <30 mg/dl; increase of total serum transferrin o of TIBC, >350 mg/dl; reduction of IS <16%; reduction of serum ferritin <10–12 ng/ml
- Increase of sTfR a 10–14 mg/l
- Reduction of reticulocyte (inconstant)
- Increase of zinc protoporphyrin > 60–80 μmol/mol-heme*
- Increase of free erythrocyte protoporphyrin (FEP) > 10 mg/dl*
- Increase of platelets count (inconstant) between 600,000–1000,000 mcL
- Rarely modest hemolysis

Parameters	Iron deficiency anemia	Hetherozygous thalassimia	Anemia of chronic diseases
MCV	Reduced	Reduced	Normal
MCH	Reduced	Reduced	Reduced
MCHC	Reduced	Normal	Reduced
RDW	Increased	Normal	Normal
Ferritin	Reduced	Normal or increased	Reduced-normal-increased
Serum iron	Reduced	Normal	Reduced
Transferrin	Increased	Normal	Reduced
Serum transferrin receptor	Increased	Increased	Normal
Tranferrin saturation index	Reduced	Normale or increased	Normal
Others	Response to iron treatment	HBA$_2$ concentration	No response to iron treatment

Table 5. Differential diagnosis of microcytic anemia.

In the diagnostic evaluation of IDA, a correct differential diagnosis must always be made with the other forms of microcytic-hypochromic anemia, such as thalassemia and anemia of chronic diseases (**Table 5**).

7. Treatment

Despite ID/IDA are well-known medical issues, this topic is not noticed adequately, and the literature contains only few publications related to iron treatment recommendations; this resulting in part from the lack of contemporary scientific literature regarding evidence-based treatment of IDA. The therapeutic approach of ID/IDA is widely variable and often suboptimal as often pediatricians administer inadequate daily doses of iron or inappropriate iron salt formulations or too short iron replacement [38]. The principles of ID/IDA management are based on some cornerstones: confirm the diagnosis, recognition and whenever possible, management of the underlying cause(s), provide adequate iron therapy, either orally or parenterally, and finally confirm the success of the treatment (correction of the hemoglobin levels and finally replenishment of body iron storage). If diet intake is inadequate, the first step is correction of the nutritional iron intake. In cases of ID or of IDA with good levels of hemoglobin, this approach may be sufficient to correct iron depletion. Usually, dietary counseling and oral iron therapy are combined.

Limited high-quality evidence supports the management of iron deficiency anemia. Oral iron replacement is preferred primarily because it is economical and has few side effects. Oral iron supplement is the treatment of choice by selecting the most appropriate compound, whereas parenteral route of administration is recommended only for selected patients. Iron-containing oral preparations currently available in the market are innumerous, with a variety of pharmaceutical forms including liquid preparations as guts, elixir, syrups, pills and effervescent tablets. Unfortunately, oral iron formulations are known to be far from ideal, mainly because of absorption and tolerability; also the palatability of the liquid preparation is often a real problem for children. Stain of teeth may occur if not thoroughly cleaned. Their chemistry is also heterogeneous, including either divalent (Fe^{2+}, or ferrous) or trivalent (Fe^{3+}, or ferric) iron, in form of iron salts or their complex-forming substrate iron. Treatment must correct hemoglobin levels and then gradually replenish iron stores. The time required varies from 3 to 6 months after the anemia is relieved. If the treatment is not continued, relapse is common. What really matter in different oral iron preparations is the content of elemental iron absorption. As a general rule, oral iron preparations do not contain more than 30% of elemental iron, but a source of confusion is represented by the fact that such proportion can vary by manufacturer, as well as in different countries. Ferrous formulations are recommended by international literature, scientific societies and international agencies as the preparations that are more effective. Ferric iron is poorly and ineffectively absorbed. The ferrous sulfate was first introduced by the French physician Pierre Blaud in the last half of 1800 and still remains the mainstay of treatment for adults as reasonable well absorbed, effective and inexpensive. Unfortunately, the tolerability of this salt is poor, making it unacceptable for many patients. Therefore, many other effective ferrous salts have been offered as ferrous gluconate, ferrous ascorbate, ferrous lactate, ferrous succinate, ferrous fumarate and ferrous glycine sulfate.

No one compound seems better than the others. Recent studies showed that ferrous bisglycinate chelate and ferrous bisglycinate chelate plus alginic acid have a good absorption at reduced doses (25–40%) in comparison with ferrous sulfate and an optimal tolerance. Unfortunately iron formulations, especially in older children and adolescent, may induce gastrointestinal discomfort mainly represented by including metallic taste, vomiting, heartburn, epigastric and abdominal pain, nausea, flatulence, dyspepsia, constipation and diarrhea. Likely due to the oxidative properties of iron on the gastrointestinal mucosa, these problems occur frequently, especially when iron is taken fasting. The stool often may turn black, which is not harmful, and treatment does not have to be interrupted. When side effects occur, iron can be taken with meals. Alternatively, smaller doses could be taken between meals. Ascorbic acid may improve the bioavailability of iron salts, but it increases the frequency of side effects. As the treatment is long, a good compliance is required for the success of the therapy. For this reason, the best tolerated preparation and schedule must be tailored for each patient in order to encourage compliance.

Standard dose is 2–6 mg/kg/day in terms of elemental iron, in 2–3 divided doses up to a maximum of 150–200 mg daily. It may be recommended to start treatment with low dose increasing day by day to full doses during 7–10 days. However, the optimum frequency of daily doses is uncertain. Single dose daily is well tolerated and effective when compared to divided dose, especially in children less than 2 years. Administration on empty stomach before sleeping seems to be more effective as decreased gastrointestinal motility of sleep enhance absorption. The absorptive capacity of iron in the duodenum is near complete saturated with about 25 mg of iron. It is conceivable that the treatment on 25 mg/day saturates the intestinal absorption capacity so that the next day doses are much less absorbed. It is interesting that in children with gastrointestinal side effects, iron administration once every other day or twice a week might be more effective than daily doses and might reduce gastrointestinal discomfort.

When patients do not tolerate full doses, a less iron dose may be administrated, but in this case, it is necessary to treat longer.

As gastrointestinal discomforts are more frequent when the stomach is empty, patients prefer to take iron immediately after or even with meal. Also, if it is clear that in this way the absorption is reduced to 30%, the better compliance to iron treatment may be preferred than a better absorbent. However, it is important to inform the patients that in this case some foods may influence iron absorption: orange juice, meat, poultry and fish enhance absorption while food high in phytates, phosphates or tannates (e.g., cereals, beans, soys, tea and milk) reduce it. The ensuing reduction of adherence, in combination with the need of prolonged treatment, results in undertreatment significant proportion of IDA patients in daily clinical practice. There has been an increasing awareness of a previously overlooked potentially negative effect of oral iron, that is, the change in gut microbiome. In the absence of ongoing blood loss or intestinal malabsorption response to iron treatment is rapid. So far, within 24 h, the child feels better, shows less irritability and an increased appetite. A peak of reticulocytes may observe at 5–7 days but routinely this re-evaluation is not performed in children to avoid discomfort. The hemoglobin measured after a month of treatment shows an increase of 1–2 g/dl. Since IDA has been treated and hemoglobin concentrations are healthy, full blood count and markers of iron status should be measured during the subsequent 6–12 months.

Treatment failure is common due to poor medication adherence, adverse effects related to excessive dosing and lack of evidence-based management guidelines. If after a month of treatment the anemia, in otherwise healthy individual, does not respond, the causes of the iron deficiency anemia must be carefully reevaluated. It is important to analyze the duration of therapy, ongoing blood loss, high gastric pH due to assumption of antacid, histamine-2 blocker, gastric acid pump inhibitor, deficit of Vitamin B12, folic acid, zinc, or hypothyroidism, a coexistent disease that interferes with iron absorption (chronic inflammation and inflammatory bowel disease or neoplasia). Finally, an incorrect diagnosis of the microcytic anemia, as thalassemia, sideroblastic anemia or genetic IRIDA as well as patients with elevated hepcidin levels driven by inflammation, must be ruled out. Unfortunately, many patients are often lost to follow-up [1–3, 22–24].

Considering the risk of adverse reaction, parenteral iron therapy should be reserved for selected patients with severe gastrointestinal absorption disorders including inflammatory bowel disease or short bowel syndrome, or when a rapid replacement of iron is required or an absolute intolerance to oral administration is demonstrated. There not indications of parenteral iron treatment for pediatric patients with celiac disease in gluten-free diet as they can absorb oral iron salt preparations with good clinical results. Of interest the observation that ferrous bisglycinate chelate is well absorbed also in patients with overt celiac disease (personal data-in press Minerva Pediatrica 2018).

The benefits of new generation parenteral formulations are greater than their risks, if adequate measures are taken to ensure the early detection and effective management of allergic reactions. Iron preparations should only be given in a protected environment, where resuscitation facilities are available in order to treat immediately. The practice of first giving the patient a small test dose is not a reliable way to predict how the patient will respond when the full dose is given. A test dose is therefore no longer recommended but instead caution is warranted with every dose of intravenous iron that is given, even if previous administrations have been well tolerated. Various iron formulations for intravenous use are now available but the approval of the products may differ in different countries. The first parenteral iron formulation was a high molecular weight iron dextran. However, intramuscular injection of iron dextran is discouraged because it is painful, produce long-standing skin discoloration, and it may be a potential risk of developing a rhabdomyosarcoma or fibrosarcoma. Intravenous administration is no longer available due to its relatively high incidence of hypersensitivity reactions. Low-molecular weight iron dextran, introduced in the 1990s is less likely to cause such reactions but the use in now is limited as formulations with improved safety profile have been licensed. Fe-gluconate (Ferlixit®) is less dangerous but is containing benzilic acid that may cause seizure in infant less than 3 years. Fe-sucrose (Venofer®) is much more expensive but represents today the best product for children considering the low risk if reacted. Finally, new and promising preparations are now under investigation but at the moment they are not approved for pediatrics: Fe-carboxymaltose (Ferrinject®), Fe-isomaltoside (Monofer®) and Ferumoxytol (Ferraheme®). Severe hypersensitivity reactions with these preparations are exceptional. Simple recommendations to minimize the risk include slow administration with careful patient monitoring during and after treatment, an adequate clinical environment with trained staff and the avoidance of

antihistamine premedication. Iron sucrose and sodium ferric gluconate are approved for both adults and children, but typically require multiple doses to achieve adequate iron replacement. For the ferric carboxymaltose, the recommended infusion time is only 15 min and is administrated once a week. It is approved in Europe and in the US for adults, not yet approved for pediatrics.

Red cell transfusion should be reserved to severe anemia, less than 5 g/dl of hemoglobin, requiring rapid correction as in children with cardiac dysfunction.

The total amount of parenteral iron to be administered may be calculated according to the following formula:

Weight (kg) × volemia (80 ml/kg) × 3.4* × g (normal Hb for age − patient Hb) × 1.5**

* 1 g of Hb alloy 3.4 mg of iron, ** correction to replenish stocks

The total dose should be divided into several administrations (initially every 2–3 days then every 1–2 weeks) to be given in a slow infusion (recommended in 1–4 h, the single dose should not exceed 5 mg/kg) [1–4, 31–40].

8. Prevention

In preterm infants (born at less than 37 weeks' gestation) the prevention of ID/IDA with the administration of iron is well-established practice, even if there is no clear evidence of benefits on long-term outcomes such as growth and neurobehavioral development. Infants who are exclusively breastfed should receive 1–3 mg/kg/day of elemental iron supplementation from 1–12 months of age, except for those who have had multiple blood transfusions; 1 mg/kg/day supplementation if using iron-fortified formula. For healthy full-term infants exclusively breastfed infants, the AAP recommends 1 mg/kg/day of iron supplementation at 4 months of age until appropriate iron-containing foods are introduced. WHO recommended daily iron supplementation with 60 mg of elemental iron to prevent iron deficiency in menstruating adolescent girls where the prevalence of anemia is about 20%.

According to the American Academy of Pediatrics, the prevention of iron deficiency is an important issue of public health and the universal screening, between 12 and 18 months, is useful to assess the possible risk factors [41–45].

9. Conclusion

Prevention and early diagnosis of ID and IDA in childhood are important to ensure normal growth and performance and to avoid possible damage on neurocognitive and behavioral development. Diagnostics are generally relatively easy and are based on the evaluation of a

few simple hematological and biochemical parameters. Treatment may have some difficulty regarding patient's compliance. So important is the role of the pediatrician in approaching the problem of iron deficiency in every phase of the intervention, from prevention, diagnosis and treatment.

Conflict of interest

The authors declares no conflict of interest.

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