Absolute Iron Deficiency in Children: Review

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Abstract: Absolute iron deficiency (A-ID) is still the most common form of malnutrition and iron deficiency anemia (A-IDA) is the most frequent kind of anemia among children/adolescents in developed countries. Prematurity, decreased dietary source, malabsorption and blood loss represent the prevalent causes of iron deficiency. A-ID and A-IDA will present with a wide variety of symptoms involving multiple organs and systems. Recent literature highlights the association between chronic A-ID and possible delayed motor, cognitive development and decreased cognitive performance. Oral iron administration remains the main treatment. The dose of elemental iron is 2–6 mg/kg/day; recent reports demonstrate that iron administration every other day is equally effective at the doses administered daily with fewer side effects. When normal Haemoglobin (Hb) values are reached, treatment must be generally continued for 3 months in order to replenish iron stores. Rarely intravenous iron administration may be necessary in some selected patients; and the new commercial products based on parenteral iron have shown a good safety profile. Prevention of A-ID might be considered as an important issue of public health.

Keywords: Iron deficiency, Iron deficiency anemia, Iron replacement.

INTRODUCTION

Despite global progress achieved in medicine and science development, nutritional anemias continue to be one of the most prevalent disorders. Absolute iron deficiency (A-ID) and absolute iron deficiency anemia (A-IDA) are serious health problems that continue to be worldwide concern. There is not a particular racial and/or ethnic group that are more likely to experience A-ID and A-IDA or hereditary factors that impact on these conditions. A low socioeconomic status continues to play a primary role in developing A-ID and A-IDA worldwide. A recent WHO report, obtained from 200 countries, showed a significant reduction in prevalence of A-ID and A-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 suffer from A-IDA. In Africa the prevalence of A-IDA among school-age children still ranges from 64.3% to 71%. Although the prevalence of IDA has decreased over the past decade, data from many surveys indicate that it remains relatively high among low-income: the prevalence of ID/IDA was 17% for 1–2 years old and 6% for 3–4 years old among Mexican American toddlers, and 12% for 1–2 years old and 5% for 3–4 years old in other low income [1-5]

In developed countries, the good health of the pediatric population and the ease of access to food has led to underestimating the onset of nutritional deficiencies, often subclinical, such as A-ID. This inattention has meant that A-ID and A-IDA are still the most common form of malnutrition among children/adolescents. In the United States, A-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). A-ID/A-IDA are less than 5% in Northern and Western Europe but is considerably higher in Eastern Europe (9-50%). In Europe, the overall prevalence of A-ID/A-IDA in childhood 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) [1-5]. A recent Italian survey, coordinated by Zuccotti (Nutrintake study), showed that most Italian children under three years of age have had a low intake of dietary iron and the European HELENA study, coordinated by Ferrari, showed the presence of reduced iron storess in 21% of girls and 17% of Italian boys [6, 7].

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Although much has already been learned about this topic, new frontiers in diagnosis and therapy emerge every day and studies are therefore needed to improve the knowledge and diagnostic-therapeutic interventions related to such a widespread disorder.

In this review we update, with additional *ad hoc* searches, the physiology, diagnosis and clinical management of A-IA and A-IDA and will try to provide pediatricians, who regularly encounter these conditions, with the main recommendations, based on the best available evidence.

PATHOPHYSIOLOGY

A detailed discussion of iron balance regulation is outside the scope of this review, and the reader is referred to some recent reviews [7-9].

Shortly, we must remember as iron metabolism is a relative "closed system" in which the majority of metal in retained within the body and continuously recycled from the hemocatheresis (about 95%) to meet the demands of the various compartments of the body, but in particularly for new red cell production. The body iron balance is managed at level of absorption by a coordinated homoeostatic process where hepcidin/ferroportin and Divalent Metal Transporter 1 (DMT-1) play a determining role. In adults less than 5% of the iron requirement is represented by that absorbed from the diet while during child development the iron requirement derives for 30-35% from the diet. It is so clear that in this age possible dietary imbalances may play a critical role in determining absolute A-ID. It is important to remember that the amount of iron absorbed is relative low compared with dietary intake (from 5 to 15% and up to more than 20% for the meal), and compensates the physiological losses (about 0.5–1 mg/day) [1-3, 6-10].

PATHOGENESIS

The pathogenesis of A-ID/A-IDA is complex. A-ID may occur in instances of decreased reserves at birth, increased demand, decreased intake (inadequate iron present in the diet or malabsorption) or chronic blood losses as shown in Table **1**.

More importantly, etiologies may vary considerably in different patient age, specific clinical conditions and various condition a may coexist in the same patient [1-3, 6-12].

In patients with inflammation the increase of hepcidin reduce iron absorption and, by holding iron from the plasma, promotes an iron deficient erythropoiesis and anemia despite adequate body iron stores (functional-ID) [1-3, 6-8]. The various etiologies of A-ID/A-IDA in children are synthesized in Figure **1**.

CLINICAL FEATURES

A-ID and A-IDA are chronic, frequently asymptomatic, and may go undiagnosed. The most

Table 1: Principal Mechanisms Leading to A-ID in Children

Decreased reserves at birth: prematurity and/or twinning, intrauterine feto-fetal transfusion in monochorionic twins and fetus-maternal bleeding, placental abnormality, exchange-transfusion at birth or severe A-IDA in the mother, early clamping of the umbilical cord
Decrease dietary iron supply: delayed complementary nutrition, incongruous diet (uncontrolled vegetarian-vegan diet), swallowing disorders, low socioeconomic status and poverty (malnutrition).
Increased demands: rapid weight-growth such as low birth weight, prematurity, adolescent development, cyanotic heart diseases.
Reduced absorption: celiac disease, intestinal bowel disease, Hirschsprung disease, large intestinal resections (short bowel), use of antacids, proton pump inhibitors and H2 blockers, excess in the diet of phytates (soy and cereals), bran, starch, calcium, polyphenols (tea and coffee), soy protein, casein and egg white, cocoa, obesity and chronic inflammatory diseases, including extra-intestinal, due to hyper-production of hepcidin, immune deficiencies with mucosal atrophy, intestinal lymphangiectasia, *Helicobacter pylori* infection, giardiasis and other intestinal parasites. Severe A-ID, because of its effect on the bowel mucosa, may induce a secondary malabsorption of iron.
Blood loss: heavy and frequent menses, Meckel's diverticulum, esophageal varices, polyps, hemorrhoids, intestinal bowel disease, intestinal parasites, recurrent epistaxis, severe hematuria, intravascular hemolysis with march hemoglobinuria, prolonged use of aspirin, cortisones, non-steroidal anti-inflammatory drugs, frequent blood sampling for diagnostic purposes (in the newborn, especially if immature, and in the small infant), defects of hemostasis, dialysis hypersensivity to whole cow's milk protein (blood loss and exudative enteropathy or leaky gut syndrome), endurance athletes, consumption more than 500 ml/day of whole cow-milk (milk protein colitis), Munchausen syndrome. Finally primary A-IDA resulting in gut alterations with blood loss aggravating existing A-ID (50% of A-IDA children have positive guaiac stools.
Hereditary forms (rare diseases): more than 60 the form identified so far as DMT1 deficiency, atransferinemia, refractory iron deficiency anemia (IRIDA)
Chronic pulmonary diseases: pulmonary hemosiderosis, cystic fibrosis, broncho-pulmonary dysplasia

important clinical manifestation of A-ID is anemia; however, considering that iron mediates over 180 biochemical reactions in different organs and tissues, it is possible for A-ID and A-IDA to present with a wide variety of symptoms involving multiple organs and systems [1-3,4-10].

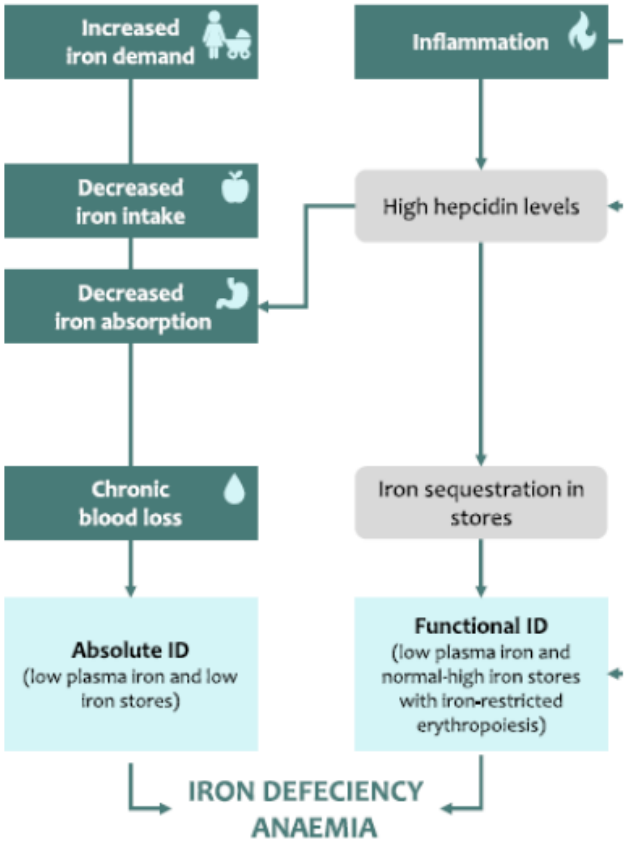

Figure 1: The various etiologies of ID/IDA in childhood (from MD.Cappelli *et al*. modified [9]).

It therefore seems suggestive to evoke the concept of <<*iron deficiency disease*>> as proposed few years ago by the Chilean Tomas Walter.

The classic clinical presentation of A-ID and A-IDA is an incidental diagnosis in a child presenting with unrelated medical problems or symptomatic A-IDA. In fact, mild A-ID, without anemia, mostly occurs asymptomatic or can only lead to poor exercise tolerance or fatigue. A-IDA usually develops slowly over a prolonged period of time and thus it is often very well tolerated by children, especially infants. Instead, typical clinical presentation of moderate to severe iron deficiency includes the usual signs of an anicteric anemia, such as pallor of skin and mucoses.

The child is 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. The pre-schooler children with A-ID may show lack of appetite, lack of desire to play and sometimes irritability; the older children may manifest listlessness, headache, reduced school performance, feeling cold and <<*restless legs syndromes*>>. Cardiac murmur and tachycardia are frequent; rarely *Angina pectoris,* hemodynamic instability and heart failure may occur in more severe forms of A-IDA. Given the high proliferative cellular activity, the mucous membranes of the gastrointestinal tract are particularly sensitive to A-ID. Glossitis, angular cheilosis, changes in the papillae of the tongue and reduced gastric acidity may appear.

Iron deficiency and chronic anemia can cause nail dystrophies, hair fragility, excess of caries, betaminuria (red color of urine after taking beetroot for greater absorption of beetroot betamine in subjects with A-ID). In long-lasting forms of A-IDA may be present growth slowdown and secondary amenorrhea.

There is conflicting information as to the effect on the of immunologic system. There is evidence of increase propensity for frequency of acute illness and respiratory infection. Reduction of lymphocytes, lymphocyte response, production of IL-2 and Il-6, phagocytic and impaired granulocyte killing and nitroblue tetrazolium activity of neutrophils may occur.In severe forms (hardly observable in our social context), we can observe picacism and/or geophagy. Modest splenomegaly may be present in 10% of patients as a result of mild hemolysis (due to increased erythrocyte membrane stiffness) [1-3, 6-8, 11, 12].

Iron is required for brain growth, myelination, monoamine neurotransmitter action, and neuronal and glial energy metabolism. Literature highlights the association between chronic A-ID and possible delayed motor and cognitive development, decreased cognitive performance with intellectual, memory, attention, learning, fine motor skills and verbal fluency deficits. This long-lasting neurocognitive impairment may be irreversible even after repletion of iron stores. Some studies have shown an association between A-ID/A-IDA and increased risk of developing stroke, idiopathic intracranial hypertension, cranial nerve paralysis, sleep disorders, febrile seizures and attention deficit and hyperactivity disorder (ADHD). Furthermore severe maternal A-IDA, may impair neurogenesis of the fetus. The mechanism underlying the impairment of nerve functions secondary to A-ID is not fully elucidated. Iron is required for proper myelination of the neurons of

sensory systems (visual, auditory) and learning and interacting behaviors. Dopaminergic neurotransmitter systems related to behavioral development (*e.g,* inhibition, affect, attention processing, and extraneous motor movements) are sensitive to changes iniron status. Iron is also a cofactor for enzymes that synthesize neurotransmitters such as tryptophan hydroxylase (serotonin) and tyrosine hydroxylase (norepinephrine, dopamine). Iron deficiency has been linked to changes in neuronal metabolism inthe hippocampus and prefrontal projections where memory processing occurs. Finally one possible hypothesis is that A-ID results in neurotransmitter alterations, iron-dependent mono-amino-oxidase deficiency and myelination defects. Iron supplementation has been hypothesized to have benefits in children that prevent possible detrimental effects of iron deficiency during development, although evidence of such effects is rather scarce [1-3, 6-8, 13, 14].

LABORATORY FINDINGS

Since A-IDA is the most common cause of anemia in children it should be prioritized in the diagnostic workup of patients presenting with anemia unless other evident mechanism are suspected.

The laboratory provides information on iron depletion (biohumoral parameters) and measures its impact on erythropoiesis (blood count and reticulocyte count) Table **2** and Table **3**.

A-IDA actually represents a late stage of iron depletion that progresses through three discernible phases. However while anemia is clearly defined as a deficiency of Hb in the blood the situation may be is ambiguous for iron deficiency [1-3, 6-8]:

a) *Pre-latent A-ID* occurs when tissue stores are depleted without change in Hb and serum iron parameters except for a moderate reduction of ferritin;

b) *Latent A-ID* that occurs when reticuloendothelial macrophage iron stores are depleted. Serum iron drops and serum transferrin increases without a change of Hb level. Serum ferritin is clearly reduced. Erythropoiesis begin to be limited by a lack of available iron. sTfR increases; Chr decreases because newly produced erythrocytes are iron deficient;

c) *AbsoluteA-IDA* is an hypochromic/microcytic anemia characterized by Hb values below the normal range for sex and age [1-3].

Detectable abnormalities biochemical parameters occur in sequence as the magnitude of A-ID worsens but so far no single measurement is currently available that will characterize the real iron status of a child.

Table 2: Red Blood Cell Parameters that Are Modified in A-IDA[1-3]

Blood smear. A-IDA is the most common cause of hypocromic-microcytic anemia. Furthermore red blood cells show variability of size and shape (aniso-poikilocytosis).
Red blood cell parameters. Are normal in A-ID but subtle change in morphologic features may be observed before than overt anemia occurs, as manifestation of iron-deficient erythropoiesis; in IDA Hb, red blood cells number and hematocrit are below two standard deviation (SD) respect normal value according to the age, gender and race. Change of red cell distribution, evaluated by red cell distribution width (RDW) and Hb distribution (HDS) usually are present before overt microcytosis (reduction of MCV) and hypochromia (reduction of MCH and MCHC) are observed. Widened RDW in association with a low MCV is one of the best diagnosis test for IDA. In general the decrease in indices parallels the decrease of Hb.
Reticulocytes count. Reticulocytes are reduced or normal. When A-IDA is associated with bleeding a reticulocyte count of 3-4% may occur. In severe forms of A-IDA may be present a low grade of hemolysis due to the rigidity of red cell membrane, than mild increase of hemolysis markers may be observed.
Reticulocyte Hb (CHr) It is parameter very useful for the diagnosis of A-ID and A-IDA. Values less than 27.5 pg for infants and toddlers and <28 pg for children and adolescent are considered very sensitive and specific. A value of CHr of less than 27.5 pg is already observed in the pre-anemic phase. Interesting, CHr concentration is not affected byinflammation, infection or malignancy
Platelets count. Thrombocytosis (600.000-1.000.000 mmc) in present in more severe form of A-IDA or when there is associated bleedings. Mild thrombocytopenia may be observed in severe and chronic A-IDA.
White blood cell. Generally they are normal. In long-lasting A-IDA a mild reduction of neutrophils may be observed.
Bone marrow. The bone marrow aspirate with the execution of Perls or Prussian blue staining allows to evaluate the accumulation of iron in the interstitium and in the medullary macrophages as well as the presence of sideroblasts. In the absence of stainable iron, a definite diagnosis of A-IDA can be made even without other laboratory tests. Although it is considered the gold standard for the diagnosis of A-IDA highly specific and widely tested, however, given its invasiveness, the need for experienced personnel and the high cost, for decades it has no longer been proposed in clinical practice neither for adults nor for children for A-IDA diagnostics.

Table 3: Clinical Laboratory Tests to Assess A-ID/A-IDA [1-3, 6-8, 15-21]

Laboratory Tests Common in Clinical Usage for A- ID/A-IDA Diagnosis
Decreased serum iron <30 mg/dl. It also decreases during acute infectious/inflammatory processes; it has wide circadian (up to 100%) and intra-individual variations and with the patient age. Serum iron may transiently increase after meat ingestion or oral iron treatment (discontinue prior to determination). Reliance on serum iron test results by general practitioners is leading to significant overdiagnosis and under diagnosis of iron deficiency in children.
Increased total serum transferrin > 350/400 mg/dl or increase in Total Iron Binding Capacity (TIBC) resulting from the calculation: TIBC (µg/dl) = Transferrin mg/dl x 1.25 (1 mg transferrin binds 1.25 µg of iron). Decreases in conditions such as infections, inflammatory states, nephrotic syndromes
Decreased transferrin saturation percentage <15%-20%
Serum iron and transferrin saturation levels, when interpreted together, provide an indication of iron use by tissue.However, recently their use in routine diagnosing A-ID/A-IDA is not supported by all experts who suggest the serum ferritin as principal or sole parameter for diagnosis
Decreased serum ferritin (SF) <12-15 ng/ml. Serum ferritin is proportional to the iron storage (1 µg/L ferritin corresponds to 8-10 mg stored iron). It is also an acute phase protein. It has diagnostic value for A-IDA only if it is decreased but does not exclude it if normal or slight increased. In fact SF concentration increases independently of the iron deposits, in situations where it behaves as an acute phase protein and as a tumor marker of inflammation, infections, and liver disease. Where these situations are clinically suspected upfront, in order to exclude possible confounding modifiers of SF, C-reactive protein (CRP)/erythrocytes sedimentation rate (ESR) must be evaluated level measurements. In case of altered CPR the SF threshold rises to 30-40 ng/ml. The same *cut-off* is also suggested for obese/overweight children/adolescents. The dosage is not very sensitive and specific during the first year of life given the wider variation in this age group. Despite these limitations SF is considered the mainstay for A-ID diagnosis, being the most sensitive and specific biomarker for assessing ID.
Increased free erythrocyte protoporphyrins (FEP). They also increase in case of infectious/inflammatory processes. The cost remains high.

TREATMENT

Despite A-ID/A-IDA are well-known medical issues, this topic is not completely noticed resulting in part from the lack of contemporary scientific literature regarding evidence-based treatment. There are no extended reports of clinical trials comparing various iron preparations, their dosage and duration. Consequently the therapeutic approach of A-ID/A-IDA results widely variable and often suboptimal.

The goal of therapy for A-ID is replenishment of body iron stores while the goal therapy for A-IDA is both correction of Hb level and replenishment of body iron stores.

Management of A-ID/A-IDA is primarily aimed at removing, whenever possible, the underlying cause of A-ID [1-3].

Nutritional Recommendations

In cases of A-ID or mild form of A-IDA due to an inadequate diet, the first step of treatment consists to improve the dietary iron intake, by educating the patient/family and providing nutritional recommendations. In many cases this approach may be sufficient to restore a normal martial set-up. In all other situations it is unlike the patient will be able to replenish iron stores without pharmacologic support [1-3, 11, 12].

Oral Products

Oral administration of iron is the usual first choice due to its excellent efficacy, safety and cost profile. Different iron-containing oral preparations are currently available, including either divalent (ferrous) or trivalent (ferric) iron with a variety of pharmaceutical forms including liquid preparations as guts, elixir, syrups, pills and effervescent tablets. The 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. The amount of elemental iron is very variable (from 10% to over 30%) from one preparation to another and represents the parameter to refer to for the prescription.

There are no reports of clinical trials comparing various oral iron preparations, their dosage, and duration. Ferrous formulations are recommended as ferric irons are poorly and inefficiently absorbed. The ferrous sulfate (FS) was first introduced by the French physician Pierre Blaud in the last half of XIX century and still remains the mainstay of treatment as reasonable well absorbed, effective and inexpensive. During FS therapy non-absorbed iron is potentially toxic for the gastrointestinal mucosa due to its oxidative properties leading to occurrence of gastro-intestinal adverse events. Side effects can occur frequently (30-70% of cases) but are never dangerous. Gastrointestinal discomfort are mainly represented by

metallic taste, vomiting, heartburn, epigastric and abdominal pain, nausea, flatulence, dyspepsia, constipation or diarrhea. Up to 40% of adult patients may self-discontinue the medication without discussing with medical doctor. No data are available for children. Therefore, in order to reduce these side effects many other effective ferrous salts have been offered as ferrous gluconate, ferrous ascorbate, ferrous lactate, ferrous succinate, ferrous fumarate and ferrous glycine sulfate. These forms generally produce fewer problems than FS; no one compound seems clearly better than the others. Generally these oral iron compounds are better tolerated than FS but may be less effective in iron replacement.

Poor compliance of iron supplementation remains the most important and common; a considerable effort should be expended to maximize compliance [1-3, 11, 12, 22-26]. Promising compounds are represented by bisglycinate chelate and by the more recent ferrous bisglycinate chelate alginate (Feralgine®). Detailed studies showed that this last compound has absolutely a better absorption in comparison with other ferrous salts (3–4 times higher than FS) and a better tolerance [27]. Our previous studies clearly demonstrated that Feralgine® is well tolerated and well absorbed also in patients with overt celiac disease, condition where all other compound fail leading to resistant form of A-IDA[28]. More common compounds of ferric iron are saccharide iron, ferromaltose, EDTA sodium iron and sucrosomial or liposomal iron [11, 12].

As the iron replacement require long time, 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 [11, 12].

Oral Products Dosages

The optimal oral iron dose is yet to be established. Traditionally recommended dose in children is 2–6 mg/kg/day once or in divide doses in term of elemental iron. In adolescents and adults recommended dose is 50–200 mg once daily or in divide doses. The optimum frequency of oral supplementation is still uncertain. It may be recommended to start treatment with low dose increasing day by day to full doses during 7–10 days [1-3, 11, 12]. Unfortunately evidence is gathering on the use of lower doses, with the aim of having equal or even superior efficacy and fewer side effects. It has been demonstrated that one day treatment saturates the intestinal absorption processes. In facta transient rise in serum iron and ferritin values that occurs immediately after oral iron administration, causes a release of hepcidin, and consequently a reduced absorption of iron. This reduced intestinal absorption, consequent to oral martial therapy, that lasts approximately 48, has been named as<<*hepcidin effect*>>. Based on this evidence, recent studies have evidenced as the administration of iron on every other day is equal or more effective than daily doses, but with less side effects [11, 12, 24-26]. Some studies indicate that also changing the administration from daily-divided to daily-single doses might reduce gastro-enteric side effects while still providing an equivalently effective iron substitution. Interesting, the search for a lower dosage of oral iron also derives from concerns on a possible negative impact of excess oral iron on the gut microbiota, favoring the nourishment of pathogenic bacteria. Furthermore administration on empty stomach before sleeping seems to be more effective as decreased gastrointestinal motility during sleep enhance absorption [1-3, 11, 12].

As gastrointestinal discomforts are more frequent when the stomach is empty, patients may 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%. It is also important to inform the parents and patients that 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 [1-3].

Response to Iron Oral Treatment

In the absence of ongoing blood loss or intestinal malabsorption, response to iron treatment is rapid and predictable. So far, within 24-48 hours, the child feels better, shows less irritability and an increased appetite. A peak of reticulocytes may be observe at 5–7 days but routinely this re-evaluation is not performed in children to avoid discomfort. More recently has been demonstrated that also CHr could be considered an affordable marker to detect early responders to oral iron therapy [30]. When therapy is fully effective the anticipated increase in Hb levels occur after 2 to 3 weeks (increase by 1–2 g/dl within 1 month) of iron treatment, and reaches normal levels by 2–3 months. When the Hb levels have been corrected, treatment should be continued for 3–4 months in order to completely fill the body iron stores. Shorter duration of treatment is associated with higher relapse rate and inadequate resolution.

The iron parameters must be monitored carefully as there has been an increasing awareness of a previously overlooked potentially negative effect of oral iron, that is, the change in gut microbiome. Since A-IDA has been treated and Hb concentrations are healthy, full blood count and markers of iron status should be measured during the subsequent 6–12 months [1-3, 11, 12].

Irrespective of the presence of anemia, once A-ID is present at least 3 months of iron replacement therapy is required [11, 12, 29].

In case of failure to respond to oral iron the principal reasons that should be considered are poor compliance, inadequate doses prescribed, ineffective iron preparation, insufficient duration, persistent or unrecognized blood loss, coexistent disease or conditions that interfere with absorption or utilization of iron [11, 12, 23, 24, 30, 31]. Oral iron absorption test may be useful [32]. 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 [1-3, 11, 12].

Parenteral Iron Replacement

The alternative for patients intolerant or unresponsive to oral compounds is IV iron. Intramuscular iron administration is never indicated in children as injection is painful, can lead to permanent skin staining and potential risk of sarcoma development at the injection sites(observed in animal models).

Parenteral iron is usually considered second-line to oral therapy in the majority of patients but the role of IV iron administration in selected children with A-IDA as a first-line therapy has been debated in the recent years. According to the recent guide lines the therapy should be reserved for patients with severe gastrointestinal absorption disorders including inflammatory bowel disease and short bowel syndrome, when a rapid replacement of iron is required, in cases of an absolute intolerance or refractoriness to oral therapy [1-3, 11, 12, 26, 33-35].

First generation IV iron preparations, as such as high molecular weight dextrans, presented with unfavorable safety profiles. Associated with severe acute reactions, they were considered unsuitable for use in pediatrics and definitely removed from the markets in 1991.Over the last three decades, there has been a significant evolution in the quality of parenteral iron products. There has been a significant increase in the evidence supporting the safety of these parenteral iron products in children over the last decade. Some iron new formulations for IV use are now currently available. Nevertheless the improved safety of the new parenteral formulations, these must be administrated in a protected environment, where resuscitation facilities are available [11, 12, 26, 33-35].

Low-molecular weight iron dextran, introduced inthe 1990s is less likely to cause adverse reactions. Ferric-gluconate is less dangerous but is containing benzilic acid that may cause seizure in infant less than 3years. Iron sucrose is much more expensive but represents today the best product for children considering the low risk of adverse effects. New and promising preparations are now under clinicalinvestigation but at the moment they are not approved for pediatrics: ferric-carboxymaltose, ferric isomaltoside and Ferumoxytol. Severe hypersensitivity reactions with these preparations are exceptional [11, 12, 25, 28]. The total amount of parenteral iron to be administered may be calculated according to the Ganzoni formula modified by Lanzkosky for children [2]:

Iron dose: body weight (kg)× blood volume (80ml / kg)× 3.4*× g (normal Hb for age−patient Hb)× 1.5**

[*1gofHballoys 3.4mgof iron: converting grams of Hb into milligrams of iron; ** Factor 1,5 provides extra iron to replenish stores]

Data from studies in adults show that IV iron is contraindicated in presence of an active/acute infection and in patients with personal history of drug anaphylaxis/allergy [11, 12, 26, 33-35].

In patients undergoing iron therapy (especially if IV) the risk of developing a iatrogenic overload must always be monitored. Finally, even if there are no data on a specific correlation between pharmacologic administration of iron and cancer, the epidemiologic reports on the possible role of iron in the onset and advance of cancer suggest caution to avoid excess iron consumption [36].

Red cell Transfusion

Red cell transfusion should be reserved to severe anemia (Hb<4-5 g/dl) requiring rapid correction as in children with risk of cardiovascular instability. Because A-IDA is slowly developing and compensatory mechanism include maintenance of intravascular volume, the risk of fluid overload when transfusing children is real. In this case the aiming is a moderate

increase in Hb purely to enable cardiac stability rather full correction to normal Hb [11, 12].

Transdermal Administration

Transdermal Administration has been experimented in animal models, but there is no evidence that it would be effective and safe in humans. However this rout of iron delivery might be a promising approach that could make a huge positive impact on patients suffering with A-ID and A-IDA [37].

PREVENTION

The American Academy of Pediatrics (AAP), considering the prevention of A-ID/A-IDA an important issue of public health, suggests an universal screening for all children at the age of 12-18 months by using Hb concentration and including evaluation of risk factors for A-ID [38]. However universal screening of IDA in children under five years of age is not recommended by other scientific societies and international agencies who recommend only selective screening in infants and children with risk factors including prematurity, low birth weight, and dietary risk factors [39-41].

In developing countries iron fortification remains the mainstay of efforts aimed toward the treatment or prevention of iron deficiency anemia. Generally iron may be provided with other micronutrients to reduce anemia in schoolchildren.

In western countries special attention must be given toward preventing iron deficiency in high risk subjects. Prevention of A-ID must be implemented already during pregnancy since maternal iron deficiency may have possible sequelae during infancy [42]. Delayed clamping (1-3 minutes) of the umbilical cord targets early infantile anemia [1-3, 11, 12]. In preterm infants (born at less than 37 weeks' gestation) the prevention of A-ID/A-IDA with the administration of oral iron (2 mg/kg/day of elemental iron, starting from one month up to one year of age) is well-established practice, even if there is no clear evidence of benefits on long-term outcomes such as growth and neurobehavioral development.

In 1971, the AAP promoted the early use of iron-fortified formulas instead of cow milk within a special program to address iron and other nutritional deficiencies. These initiatives have had a tremendous impact on the health of children. For instance, in one review including children aged 6-60 months, the prevalence of anemia declined from 7.8% in 1975 to 2.9% in 1985 [38]. Furthermore for healthy full-term infants exclusively breastfed infants, the AAP recommends 2 mg/kg/day of iron supplementationand1 mg/kg/day supplementation if using iron-fortified formula, at 4 months of age until appropriate iron-containing foods are introduced [1-3, 11, 12, 38-40]. An iron supplementation (60 mg of elemental iron) is also recommended in menstruating adolescent girls [1-3, 38-40].

Certain populations do not benefit from universal iron supplementation. With inherited hemochromatosis, the absorption of dietary iron increases. Some genetic variants are quite common, especially in northern Europeans. Although the clinical penetrance is quite variable in the most common forms of hereditary hemochromatosis, communal iron fortification for this group is generally not recommended [43].

CONCLUSIONS

Prevention and early diagnosis of A-ID and A-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. However consideration of A-ID/a and A-IDA must include the possible convergence of several causative factors. Basic treatment is oral iron administration but it may have some difficulty regarding patient compliance. IV treatment should be chosen on once a clear indication is met.

The role of the pediatrician in approaching the problem of A-ID and A-IDA in every phase of the intervention, from prevention, diagnosis and treatment is crucial for the well-being of the child. Of course, as pediatric medicine is an ever-changing field, it is the responsibility of the treating pediatrician who relies on experience and knowledge about his/her patient to determine the best diagnostic or treatment for his/her patient. Also if this topic is known for a long time, it is constantly developing with accumulation of new knowledge the practicing pediatrician requires rapid access to evidence-based and updated informations to make timely diagnoses and offer accurate treatment for common conditions. The present review has been intended to provide a useful contribution with a concise but thorough description of the major causes, diagnostic and therapeutic procedures of A-ID and A-IDA. Finally, this practical approach might help to promote a full compliance with patients and their parents to prevention and treatment of these conditions.

CONFLICT OF INTEREST

The authors have not conflicts of interest to declare.

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