



**Review Article**

**Iron Deficiency Anemia in Children Residing in High and Low-Income Countries: Risk Factors, Prevention, Diagnosis and Therapy**

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**Competing interests:** The authors declare no conflict of Interest.

**Abstract.** Iron deficiency and iron-deficiency anemia (IDA) affects approximately two billion people worldwide, and most of them reside in low- and middle-income countries. In these nations, additional causes of anemia include parasitic infections like malaria, other nutritional deficiencies, chronic diseases, hemoglobinopathies, and lead poisoning. Maternal anemia in resource-poor nations is associated with low birth weight, increased perinatal mortality, and decreased work productivity. Maintaining a normal iron balance in these settings is challenging, as iron-rich foods with good bioavailability are of animal origin and either expensive and/or available in short supply. Apart from infrequent consumption of meat, inadequate vitamin C intake, and diets rich in inhibitors of iron absorption are additional important risk factors for IDA in low-income countries. In-home iron fortification of complementary foods with micronutrient powders has been shown to effectively reduce the risk of iron deficiency and IDA in infants and young children in developing countries but is associated with unfavorable changes in gut flora and induction of intestinal inflammation that may lead to diarrhea and hospitalization. In developed countries, iron deficiency is the only frequent micronutrient deficiency. In the industrialized world, IDA is more common in infants beyond the sixth month of life, in adolescent females with heavy menstrual bleeding, in women of childbearing age and older people. Other special at-risk populations for IDA in developed countries are regular blood donors, endurance athletes, and vegetarians. Several medicinal ferrous or ferric oral iron products exist, and their use is not associated with harmful effects on the overall incidence of infectious illnesses in sideropenic and/or anemic subjects. However, further research is needed to clarify the risks and benefits of supplemental iron for children exposed to parasitic infections in low-income countries, and for children genetically predisposed to iron overload.

**Keywords:** Low income countries; Developed countries; Prevention; Therapy; Iron deficiency; Iron deficiency anemia.

**Citation:** Mantadakis E., Chatzimichael E., Zikidou P. Iron deficiency anemia in children residing in high and low-income countries: risk factors, prevention, diagnosis and therapy. *Mediterr J Hematol Infect Dis* 2020, 12(1): e2020041, DOI: <http://dx.doi.org/10.4084/MJHID.2020.041>

**Published:** July 1, 2020

**Received:** May 5, 2020

**Accepted:** June 12, 2020

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**Introduction.** Iron deficiency anemia (IDA) is by far the most common anemia worldwide. World Health Organization (WHO) estimates that close to two billion people or 25% of the world's population are anemic,

and approximately half of them suffer from IDA.<sup>1</sup> Besides, for every patient with IDA, there is at least one more with iron deficiency without anemia. Therefore, there are more than two billion people with iron deficiency with or without anemia, and most of them reside in resource-poor countries.<sup>2</sup> Additional causes of anemia in low-income countries include other nutritional deficiencies (vitamin B12, folic acid, riboflavin), chronic diseases, parasitic infections like malaria, hemoglobinopathies, and lead poisoning.<sup>3</sup> Anemia is a significant cause of maternal deaths and adverse pregnancy outcomes in developing countries. A recent meta-analysis showed that 42.7% of women in low- and middle-income countries experienced anemia during pregnancy, and this was associated with significantly higher risks of low birth weight, preterm birth, perinatal and neonatal mortality. South Asian and African countries had the highest pooled anemia prevalence. Overall, 12% of low birth weight, 19% of preterm births, and 18% of perinatal mortality were attributable to maternal anemia.<sup>4</sup>

Nevertheless, IDA is also frequently identified in certain high-risk groups in developed countries, like infants and toddlers, adolescent females, women of childbearing age, and the elderly. In industrialized countries, iron deficiency is the only frequent micronutrient deficiency.<sup>5</sup> In the U.S., it is estimated that at least 2.7% of toddlers one to two years old suffer from IDA.<sup>6</sup> A review of 44 studies conducted in 19 European countries showed that 2-25% of infants aged 6-12 months were iron deficient, with a higher prevalence in those who were socioeconomically deprived and in those who were drinking cow's milk during their first year of life. In children aged 12-36 months, prevalence rates of iron deficiency varied between 3% and 48%, while the prevalence of IDA in both age groups was up to 50% in Eastern but below 5% in Western Europe.<sup>7</sup> On the other hand, up to 40% of preschool children in low- and middle-income countries are estimated to be iron deficient and/or anemic.<sup>8</sup> Special populations at risk for IDA in developed countries include indigenous people, newly arrived immigrants, refugees, regular blood donors, endurance athletes and vegetarians.<sup>9,10</sup>

IDA is the ultimate result of untreated iron deficiency, and globally iron deficiency ranks number nine among 26 modifiable risk factors for death included in the Global Burden of Disease project.<sup>11</sup> Regardless of the presence of symptoms, patients with IDA should be treated as early as possible because they are at risk for organ ischemia and further worsening of the anemia unless the underlying cause is relieved, and the bone marrow iron stores refilled. Likewise, children with iron deficiency alone should be treated because sideropenia is associated with long-lasting neurocognitive impairments, decreased learning ability, and altered motor function.<sup>12,13</sup> Febrile seizures, breath-

holding spells, and restless leg syndrome have also been shown to be much more prevalent in people with iron deficiency.<sup>14-16</sup> In adolescent and young adult females, isolated iron deficiency is associated with fatigue and cold intolerance that is relieved with appropriate oral iron therapy.<sup>17</sup>

The worldwide prevalence of anemia has slightly decreased in the past 20 years, but the situation remains concerning in Central and Western Africa.<sup>1</sup> In the U.S., despite the decline in iron deficiency prevalence among infants, black, and underprivileged children, iron deficiency prevalence did not change much in toddlers between 1976 and 2002 and remained high in certain groups such as Hispanic, younger and overweight toddlers.<sup>18</sup> In developing countries, the prevalence of anemia (not just IDA) in younger children is close to 50%, and as previously said, about half of this anemia is considered to be due to iron deficiency.<sup>1</sup> This proportion is lower in countries with anemia prevalence more than 40% (see below) and in countries with a very high burden of infectious diseases, where inflammation is a primary contributor to anemia. In developed countries and beyond the fifth year of life, IDA is less common in children of school age and becomes a frequent problem again in adolescent females with heavy menstrual bleeding, pubertal growth spurt, and poor diets,<sup>19</sup> as well as in women of childbearing age and older people.<sup>20</sup>

**Dietary Absorption of Iron.** Hemoglobin contains approximately 65-75% of the total body iron in the form of heme. Another 10-20% is stored in the form of ferritin and hemosiderin; about 4% is contained in myoglobin, 3-4% in various enzyme systems, and around 2% is in a labile pool that forms reactive oxygen species.<sup>21</sup> Most of the circulating iron comes from the recycling of senescent erythrocytes. However, a small but critical amount (1-2 mg per day) is absorbed daily from the diet in order to compensate for gastrointestinal and other iron losses such as sweating and skin sloughing.

Dietary iron exists in two forms, i.e., as heme iron derived from hemoglobin and myoglobin in meat and as nonheme iron that can be extracted from plants and dairy foods. The bioavailability of heme iron is substantially higher (up to 25%), but even in developed countries, most dietary iron is absorbed in the form of nonheme iron. The bioavailability of the latter is only 5-10% and is adversely affected by consumption of phytates in cereals and vegetables, and the consumption of polyphenols, tannins, and oxalates that are contained in vegetables, some fruits, legumes, coffee, and tea. Vitamin C increases the absorption of dietary iron.<sup>22</sup> **Table 1** shows plant foods that reduce iron absorption, while **Table 2** displays the daily recommended iron requirements by age.<sup>23</sup>

IDA results from a reduction of the body's iron

**Table 1.** Plant foods that reduce iron absorption.

<b>Oxalate-rich foods</b>	Beverages: Coffee, tea (especially black tea) Cereals: Wheat bran Chocolate Fruits: Strawberries Herbs: Rhubarb, oregano, basil, parsley Vegetables: Beans, beets (roots and leaves), celery, spinach, kale Nuts: Peanuts Oilseeds: Soybeans
<b>Polyphenol-rich foods</b>	Beverages: Coffee, green tea, black tea, red wine, cider Cereals: Corn, wheat, rice, oat Cocoa Fruits: Apples, blackberries, raspberries, blueberries, black currant, strawberry, kiwi, cherry, plum, pear, apricot, peach, black grape, red grape Herbs: Rhubarb, peppermint, parsley Vegetables: Potato, red cabbage, yellow onion, tomato, broccoli, beans, green or white, chicory, artichoke, curly kale, leek, celery, capsicum pepper Nuts: Walnuts Oilseeds: Soybeans Spices
<b>Phytate-rich foods</b>	Cereals: Wheat, oats, rice, corn (maize), barley, sorghum, rye, millet, soybean Nuts: Walnuts, peanuts, almonds, cashew nuts Oilseeds: Soybeans, linseed, sesame seed, sunflower meal Vegetables: Dried beans, lentils, peas, chickpeas
<b>Calcium-rich foods</b>	Fruits: Figs Herbs: Rhubarb Nuts: Almonds Oilseeds: Soya beans Vegetables: Broccoli, cabbage, okra, turnip greens, beans, kale

**Table 2.** Recommended dietary allowance (RDA) for iron by age (modified from reference 23).

Both sexes	RDA in mg/day
<1 year	6-10
1-2 years	10
3-5 years	10
<b>Females</b>	
6-11 years	10
12-19 years	15
20-29 years	15
30-39 years	15
40-49 years	15
50-59 years	10
60-69 years	10
≥70 years	10
<b>Males</b>	
6-11 years	10
12-19 years	12
20-29 years	10
30-39 years	10
40-49 years	10
50-59 years	10
≥60 years	10

content due to blood loss, inadequate iron supply, decreased absorption of iron, or a combination of the above factors. Inflammation diverts iron from the bone marrow, where erythropoiesis takes place to storage sites of the reticuloendothelial system in the liver and spleen, leading to iron-restricted erythropoiesis and anemia. The peptide hepcidin is the master regulator of intestinal iron absorption and tissue iron distribution by inducing degradation of the cellular iron exporter ferroportin.<sup>24</sup> Ferroportin transfers iron into plasma after its absorption from the basolateral surface of the enterocytes, and stored iron from macrophages and hepatocytes that recycle heme from senescent erythrocytes. Any infectious disease and/or inflammatory condition upregulates hepcidin expression through interleukin 6 (IL-6) and decreases iron absorption. The upregulated IL-6 is responsible for the characteristic hypsideremic response to acute inflammation.<sup>25</sup> Hence, chronic heart failure, chronic kidney disease, inflammatory bowel diseases, autoimmune rheumatic diseases, and obesity—a frequently overlooked inflammatory condition that is almost exclusively limited in developed countries—are associated with decreased iron absorption. Hepcidin blood levels are indeed higher in obese than normal-weight individuals, and this limits iron absorption, hinders iron fortification and leads to increased sequestration of iron in macrophages.<sup>26</sup>

**Risk Factors and Prevention of IDA.** WHO defines anemia in a population as a mild, moderate, or severe public health problem if its prevalence is 5-20%, 20-40%, or >40%, respectively.<sup>1</sup> Most of the WHO countries have a moderate-to-severe public health problem with anemia, i.e., over 20% of women and young children are affected. In developing countries, diets with poor iron bioavailability are the primary cause of IDA.<sup>27</sup> In these countries, the leading cause of IDA is not so much the diet's poor iron content, but its rather poor bioavailability, since it comes from plant sources rich in inhibitors of iron absorption.<sup>28</sup> In most low-income countries, rural diets are based predominantly on cereal- or legume-based flours that are often rich in phytates, and many common foods or beverages contain iron-binding phenols, whereas consumption of meat, poultry, and fish, which are rich in iron and zinc is often low because of economic, cultural and/or religious reasons. Maintaining an adequate iron balance in resource-limited settings is difficult due to poverty since iron-rich foods with high iron bioavailability are of animal origin and either expensive and/or available in short supply. Infrequent, i.e., ≤2 times per week consumption of red meat, inadequate vitamin C intake, frequent tea consumption, and high dietary consumption of phytates and polyphenols are risk factors for IDA that are mainly found in countries with limited resources.

Under these circumstances, the fortification of foods with iron is considered as the most cost-effective approach in reducing the prevalence of iron deficiency and its anemia. Fortification of foods implies the addition of iron-containing substances to the product recipe, either as isolated compounds (e.g., iron salts or chelates) or as iron-rich ingredients (e.g., meat or its derivatives). The choice depends on the desired product characteristics, including taste and color, and maybe restricted by cost and availability. Because of iron's oxidation-reduction properties, it can lead to chemical instability in the food matrix. Thus, the industry uses insoluble, poorly soluble, or strongly chelated iron compounds, all of which have limited chemical reactivity. However, both solubility and chemical availability are necessary for the effective absorption of nonheme iron.

WHO guidelines suggest in infants and toddlers 6-23 months of age fortification of complementary foods with iron-containing micronutrient powders (MNPs), which should include 12.5 mg of elemental iron per sachet, preferably as coated ferrous fumarate, corresponding to 37.5 mg of ferrous fumarate or 62.5 mg of ferrous sulfate heptahydrate or other equivalent amounts in the various iron compounds. In children 6-12 months old, sodium iron EDTA (NaFeEDTA) is not recommended. The same guidelines suggest fortification of complementary foods with iron-containing MNPs in children 2-12 years, including 12.5 mg of elemental iron for children aged 2-4 years and 12.5 to 30 mg elemental iron for children 5-12 years of age.<sup>29</sup> If NaFeEDTA is selected as a source of iron, the dose of elemental iron should be reduced by 3-6 mg due to its higher bioavailability. The UNICEF's MNP product contains 10 mg of iron per sachet, as coated ferrous fumarate, NaFeEDTA or ferrous bis-glycinate.<sup>30</sup>

In-home iron fortification of complementary foods with MNPs has been shown to effectively reduce the risk of iron deficiency in children less than two years of age in low-income countries without changing their customary diet.<sup>31</sup> Unfortunately, MNPs are associated with unfavorable changes in gut flora and induction of intestinal inflammation that may lead to diarrhea and increased risk of hospitalization.<sup>32,33</sup> Moreover, the benefits of this intervention on survival or the developmental outcomes of infants and toddlers are unclear.<sup>34</sup> Thus, MNPs cannot be considered as an ideal substitute for meat.

Another major problem with universal iron fortification is the risk of iron overload in people with hereditary hemochromatosis and hemoglobinopathies. Hereditary hemochromatosis is the most common autosomal recessive disorder in Caucasians, with a prevalence of 1 in 300 to 500 individuals.<sup>35</sup> The worldwide frequency of the H63D mutation in the HFE protein is about 8.1%, and of the C282Y mutation

1.9%.<sup>36</sup> Men are affected with hemochromatosis around 2 to 3 times as often as women, and iron overload usually appears after the age of 40 years in men and after the age of 50 years in women because menstruation increases iron removal. Hemochromatosis has the same prevalence in Europe, Australia, and other Western countries, but is less common among patients of African descent. Thus, Caucasians have a six times higher risk of developing the disease than blacks. Therefore, universal iron fortification of foods may be safe in Africa but might be hazardous in countries with a predominantly Caucasian population, although more research is needed to confirm or refute this concern.

In developed countries, dietary mistakes and gastrointestinal and genital blood loss are the most common etiologies of IDA. In industrialized nations, incorrect dietary habits such as prolonged breastfeeding without iron supplementation beyond the fourth month of life, decreased consumption of iron-fortified milk, the introduction of fresh cow's milk before the first birthday, cow's milk consumption > 500 mL/day, daytime bottle use beyond the twelfth month of life, bottle use in bed, preferred consumption of poultry over red meat, and vegan diets are associated with IDA. Moreover, celiac disease, symptomatic giardiasis, gastrectomy, decreased gastric acidity, and inadequate oral iron intake for cultural or religious reasons are causes of iron deficiency and IDA through decreased iron supply.<sup>37,38</sup> On the other hand, prolonged and/or heavy menses, use of intrauterine devices over contraceptive pills for birth control, traumatic or operative blood loss, blood donation, inflammatory bowel diseases, gastrointestinal bleeding due to antithrombotic, antiplatelet or non-steroidal anti-inflammatory drugs and congenital or acquired bleeding disorders predispose to iron deficiency and IDA due to blood loss. In all countries, long-lasting *Helicobacter pylori* infections,<sup>39</sup> and in developing countries, hookworm infestation and schistosomiasis are additional risk factors for IDA. Regarding hookworm infection, it is one of the most common tropical diseases in the world, and despite its frequent association with IDA in developing countries, it often remains untreated.<sup>40</sup> Iron refractory iron deficiency anemia (IRIDA) is a rare autosomal recessive disorder of iron metabolism characterized by IDA unresponsive to oral iron but partially responsive to parenteral iron therapy.<sup>41</sup> IRIDA is caused by mutations in the TPMRSS6 gene and is a very infrequent cause of IDA in all countries.<sup>42</sup> **Table 3a** summarizes known risk factors for IDA based on etiology and **Table 3b** main risk factors for IDA in low-and high-income countries.

Although the total body iron content is regulated by iron absorption and is highly conserved, rapid body growth, menstruation, and pregnancy require additional iron supply. Premature neonates are also frequently iron deficient because most of the iron accumulates

**Table 3a.** Risk factors for IDA by cause.

<p><b>3.1 Increased iron demands</b>  Prematurity  Infancy  Adolescence, especially in females  Pregnancy  Lactation  Regular blood donation  Competitive athletics</p> <p><b>3.2 Diminished iron supply</b>  Prolonged breastfeeding without iron supplementation beyond the fourth month of life  Consumption of infant formula low in iron  Introduction of fresh cow’s milk before the first birthday  Daytime bottle use beyond the twelfth month of life  Bottle use in bed  Preferred consumption of poultry over red meat, vegan and vegetarian diets</p> <p><b>3.3 Blood loss</b>  Traumatic or operative blood loss  Gastrointestinal bleeding: Inflammatory bowel diseases (IBDs), stomach cancer, colon cancer, colonic polyps, non-steroidal anti-inflammatory drugs, chronic <i>Helicobacter pylori</i> infection, hookworm infection, angiodysplasia  Gynecological bleeding: Menorrhagia, uterine fibroids, endometrial carcinoma, use of intrauterine devices over contraceptive pills for birth control  Urological bleeding: Schistosomiasis, bladder cancer, glomerulonephritis, kidney trauma  Pulmonary bleeding: Lung tuberculosis, congenital lung malformations, lung cancer, idiopathic pulmonary hemosiderosis, Goodpasture’s syndrome, etc.  Bleeding diathesis (congenital or acquired)</p> <p><b>3.4 Malabsorption of iron</b>  Celiac disease (gluten sensitive enteropathy)  Atrophic gastritis, gastric surgery  Decreased gastric acidity (e.g., antacids, H2 blockers, proton-pump inhibitors)  Iron Refractory Iron Deficiency Anemia (IRIDA)</p>
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**Table 3b.** Main risk factors for IDA in low-income and developed countries.

Low-income countries	Developed countries
Prolonged breastfeeding without iron supplementation beyond the 4 <sup>th</sup> month of life	Gastrointestinal bleeding of any etiology as per Table 3a
Limited consumption of meat and fish	Genitourinary bleeding of any etiology as per Table 3a
Diets rich on cereal- or legume-based flours, excess of dietary fiber	Iron malabsorption of any etiology as per Table 3a
Inadequate vitamin C intake, frequent consumption of coffee and tea	
Multiparity	
Hookworm infestation	
Schistosomiasis	
Malaria (contributes to IDA by causing intravascular hemolysis with hemoglobinuria)	
Chronic or repeated infections (functional iron deficiency due to chronic inflammation)	

during the third trimester of pregnancy. Thus, the prevention of IDA in children is feasible by avoiding breastfeeding without the administration of iron supplements beyond the fourth month of life, in addition to using infant formulas high in elemental iron (>6.7mg/L) and consuming meat products.<sup>8</sup> Delayed cord clamping increases the neonate’s body iron stores and may decrease the risk of IDA in the first six months of life.<sup>43</sup> Consumption of large amounts of fresh cow’s milk by infants and toddlers negatively affects their iron stores because of its low iron content, the frequent occurrence of occult gastrointestinal bleeding associated with cow’s milk, and the inhibition of nonheme iron absorption by the casein and calcium

of milk.<sup>44</sup>

For the prevention of IDA, the American Academy of Pediatrics recommends infants born at <37 weeks’ gestation who breastfeed should receive elemental iron at 2 mg/kg/day, as medicinal iron or iron-fortified milk or complementary foods starting after the first month and extending through twelve months of life. Exclusively breastfed term infants should receive an iron supplement of 1 mg/kg/day, starting at four months and continued until iron-containing complementary foods have been introduced. Term infants who receive iron-fortified formula do not require medicinal iron unless they have other risk factors for IDA.<sup>12</sup> Properly fed toddlers do not require

medicinal iron supplements in developed countries. However, if the diet has low iron content, medicinal or over the counter supplements containing iron alone or along with vitamins and other minerals are effective.

**Diagnosis of IDA.** Anemia is usually defined as hemoglobin <11g/dL in infants and toddlers 6 months to 5 years old, hemoglobin <11.5g/dL for children 5-12 years old and hemoglobin <12 g/dL for adolescent females > 12 years old (<13g/dL for adolescent males).<sup>45</sup> IDA is a microcytic and hypochromic anemia, i.e., is characterized by a low mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). In addition, there is low red cell count, elevated red cell distribution width, a measure of the variation of red blood cell size (anisocytosis), along with a low reticulocyte count or reticulocyte production index, low hemoglobin A<sub>2</sub> and frequent thrombocytosis. IDA, along with infections, is the most common cause of an elevated platelet count worldwide.<sup>46</sup> In a pediatric study, MCH <25 pg was also more likely to predict a significant hematologic response to oral iron therapy than an MCV of <75 fL.<sup>47</sup>

From a biochemical perspective, IDA is characterized by low serum iron, low serum ferritin, decreased transferrin saturation, increased total iron-binding capacity, elevated soluble serum transferrin receptors (sTfR), elevated serum zinc protoporphyrin (ZnPP) and low serum hepcidin-25, the active form of hepcidin. Ferritin can be misleading in children with IDA and concurrent infections, as it is an acute-phase protein. Unfortunately, measurements of sTfR and ZnPP are not widely available and are expensive, while hepcidin is almost exclusively used for research purposes considering the lack of a gold standard measurement assay and pending resolution of the international efforts for harmonization.<sup>48</sup>

In the last two decades, the percentage of hypochromic erythrocytes and especially CHr (hemoglobin content of reticulocytes or RET-He) have emerged as reliable indicators of IDA and response to iron therapy.<sup>49,50</sup> CHr measures the functional iron available for erythropoiesis over the previous three days and is an early indicator of iron-restricted erythropoiesis, i.e., the second stage of iron deficiency before the development of overt anemia. Moreover, CHr, unlike ferritin, is not affected by inflammation. A pediatric Italian study showed that CHr along with absolute reticulocyte count was able to detect among patients with IDA the early responders to oral iron therapy so that unresponsive children could be offered alternative therapies.<sup>51</sup>

**Table 4** summarizes the standard hematologic and biochemical features of IDA. It should be emphasized that the estimates of the prevalence of iron deficiency and IDA that are available from low-income countries

**Table 4.** Hematologic and biochemical features of IDA.

<p><b>Hematologic features of IDA</b></p> <p>Low reticulocyte count and reticulocyte production index (reticulocytes% X patient's hematocrit/normal hematocrit X 0.5) (&lt;0.5%)</p> <p>Low red cell indexes*</p> <ul style="list-style-type: none"> <li>-Low mean corpuscular volume (MCV)</li> <li>-Low mean corpuscular hemoglobin (MCH)</li> <li>-Low mean corpuscular hemoglobin concentration (MCHC)</li> </ul> <p>Low red cell count*</p> <p>Elevated red cell distribution width (RDW-CV) (&gt;15%)</p> <p>Low hemoglobin content of reticulocytes (CHr) (&lt;26pg)</p> <p>Low-normal hemoglobin A<sub>2</sub> (1.5-3.2%)</p> <p>Elevated platelet count (thrombocytosis) (&gt;400,000/<math>\mu</math>L)</p> <p><b>Biochemical features of IDA</b></p> <p>Low serum iron (&lt;40<math>\mu</math>g/dL)</p> <p>Low serum ferritin (&lt;20<math>\mu</math>g/L, &lt;100<math>\mu</math>g/L if functional iron deficiency or sequestration is present as in chronic inflammatory disorders or malignancies)</p> <p>Increased serum transferrin (&gt;400<math>\mu</math>g/dL)</p> <p>Low transferrin saturation (&lt;20%)</p> <p>Increased serum zinc protoporphyrin (&gt;40<math>\mu</math>mol/mol)</p> <p>Increased soluble transferrin receptors (sTfR) (&gt;35nmol/L)</p> <p>Low serum hepcidin-25 (reference values are assay-dependent and vary among laboratories since a gold standard is still lacking)</p>
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\*reference values are dependent on age and sex

are mostly indirect since only hemoglobin is measured with simple field-based techniques, while ferritin or other indicators of iron status are not routinely determined due to cost.

**IDA Screening Recommendations.** It is questionable whether screening programs for IDA are cost-effective. In low-income countries where IDA is rampant, universal iron supplementation will likely utilize the limited financial resources more prudently compared to a hemoglobin screening approach. Nosratnejad et al. using data from five medical databases showed that there is not enough evidence of cost-effectiveness for screening.<sup>52</sup> Moreover, since only about half of all anemia cases worldwide are due to iron deficiency, screening with hemoglobin alone, i.e., without biochemical indicators of iron deficiency is inadequate for diagnosis of IDA.

WHO recommends targeted screening for IDA in children and pregnant women prior to iron administration if anemia prevalence is >5% and guidelines for the management of iron-deficient patients exist.<sup>53</sup> The American Academy of Pediatrics recommends universal screening of infants for IDA at one year of age because it considers the condition to be highly prevalent and easily treatable.<sup>12</sup> In contrast, the U.S. Preventive Services Task Force considers there is insufficient evidence to recommend for or against routine screening for IDA in asymptomatic children 6-12 months old but recommends such screening in all pregnant women.<sup>54</sup> Finally, the Centers for Disease Control and Prevention recommends targeted screening for selected children at high-risk for IDA, such as

premature infants, infants living in poverty, refugees, those fed a low-iron or unfortified formula, or who continue to breastfeed without iron supplementation after six months.<sup>23</sup> We also believe that targeted rather than universal screening for IDA may be more cost-effective, but high-quality scientific evidence is clearly missing.

### Treatment of IDA with Oral Iron Products.

Medicinal iron exists in reduced ferrous (bivalent, Fe<sup>2+</sup>) and oxidized ferric (trivalent, Fe<sup>3+</sup>) forms.<sup>55,56</sup> In all oral iron medicinal products, iron has to be reduced to the ferrous form in order to be absorbed. As a heavy metal, iron is able to form salts quickly when combined with various anions, and several of these compounds are used therapeutically. Many oral iron preparations are available for the treatment of IDA, but ferrous sulfate (F.S.) is by far the most widely used oral iron product worldwide. **Table 5** summarizes available oral iron products. As shown, there are ferrous iron salts, ferric iron salts, heme-iron polypeptides, carbonyl iron, chelates of iron with amino acids, complexes of ferric iron with polysaccharides (iron polysaccharide complex, IPC), and complexes of iron with amino acids in casein, such as iron protein succinylate and iron acetyl aspartylate. These latter two products are well-tolerated but are substantially more expensive compared to iron salts or IPC. Sucrosomial iron represents a new state-of-the-art oral iron-containing carrier in which ferric pyrophosphate is enclosed by a phospholipid bilayer membrane, made from sunflower lecithin, while further gastrointestinal stability is obtained by adding tricalcium phosphate and starch for the formation of the “sucrosome”.<sup>57</sup> Sucrosomial iron, is directly absorbed by the Microfold cells, also known as M cells of the small intestine and reaches the liver via the lymphatic system. Thus, it completely bypasses the conventional iron absorption pathway and is carried through the gut without untoward side effects from the lack of interaction with the intestinal mucosa. Other studies in animal models of iron solid lipid nanoparticles prepared by hot homogenization/ultrasonication of F.S. in different solid lipids and of ferritin-core mimetics, i.e., nanoparticulate tartrate-modified ferric poly oxo-hydroxide also reveal enhanced bioavailability.<sup>58,59</sup>

Oral iron supplementation in third world countries is associated with increased risk of parasitemia in children with malaria, but this side effect is insignificant in areas where concrete malaria surveillance and control exist.<sup>60</sup> Moreover, a systematic review of 28 randomized controlled clinical trials of iron supplementation or fortified formula milk or cereals in children did not show any apparent harmful effect on the overall incidence of infectious illnesses, although it slightly increased the risk of diarrhea.<sup>61</sup>

Oral iron supplements acutely elevate serum

**Table 5.** Available oral iron medicinal products for prevention and treatment of iron deficiency and IDA.

<ul style="list-style-type: none"> <li>-Ferrous (Fe<sup>2+</sup>) iron salts: Ferrous sulfate, ferrous gluconate, ferrous fumarate, ferrous acetate, ferrous ascorbate</li> <li>-Ferric (Fe<sup>3+</sup>) iron salts: Ferric citrate</li> <li>-Heme iron polypeptides</li> <li>-Carbonyl iron (available in oral suspension and in tablets with iron alone or combined with folic acid, zinc, vitamin C, vitamin B12 in various combinations)</li> <li>-Iron chelates with amino acids: Ferrous bis-glycine chelate, ferric tris-glycine chelate, ferrous bis-glycinate hydrochloride, ferric glycinate</li> <li>-Iron (Fe<sup>3+</sup>) hydroxide polymaltose complex</li> <li>-Sucrosomial iron, other forms of liposomal oral iron</li> <li>-Iron protein succinylate, iron acetyl aspartylate</li> </ul>
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hepcidin levels, but the duration and extent of the increase, its dependence on the administered iron dose, and its effects on iron absorption have only recently been studied in humans. Moretti et al. recruited 54 iron-deficient but non-anemic young women. By using radiolabeled iron, they showed that with increasing dose, the fractional absorption of oral iron significantly decreased, while absolute absorption increased. A six-fold increase in iron dose, i.e., from 40 to 240 mg, resulted in only a threefold increase in iron absorption. Providing lower doses, i.e., 40 to 80 mg of elemental iron and avoiding twice-daily dosing, maximized fractional absorption.<sup>62</sup> These results were confirmed by two studies funded by the Swiss National Science Foundation that showed that in iron-depleted women, the administration of iron supplements daily as divided doses increases serum hepcidin and reduces iron absorption.<sup>63</sup> Hence, providing iron supplements in single doses and on alternate days optimizes iron absorption and might be a better dosing regimen, although further investigations are required in anemic, not just sideropenic patients.

Several issues require consideration when choosing oral iron therapy. First, a product with good bioavailability needs to be chosen. Second, a clinically effective and well-tolerated dose should be used. Finally, the number of daily doses should be minimized in order to improve compliance with lengthy oral iron therapy. Unless the patient continues to bleed or cannot adequately absorb iron, oral iron therapy is expected to increase the hemoglobin after two to three weeks with full correction of IDA by two months unless the anemia was particularly severe at the start of therapy. A less than 1 g/dL increase in hemoglobin after two weeks of therapy is a frequently used criterion for assessing response to oral iron therapy,<sup>64</sup> although, in all patients with IDA, oral therapy should be continued for several months after anemia is corrected to replenish body iron stores.<sup>65</sup>

The existing dosing recommendations for all oral iron products in children are mainly empirical. Few clinical studies exist comparing different oral iron products. Kruske et al. performed a randomized,

unblinded clinical trial in children < 6 years of age with anemia in an aboriginal community in Australia. Oral F.S. was prescribed at 3 mg/kg/day as a single daily unsupervised dose and was compared to twice weekly supervised administration over three months. Remarkably enough, oral F.S. as directly observed twice-weekly treatment was superior to unsupervised daily therapy.<sup>66</sup> Zlotkin et al. performed a randomized study of liquid F.S. for two months in 557 anemic children aged 6-24 months in rural Ghana. Patients received 40 mg of elemental iron once daily versus 40 mg in three divided doses. Successful treatment of IDA occurred in 61% of those receiving a single dose versus 56% of the three times daily group. Side effects were minimal and did not differ between the two groups.<sup>67</sup> Bopche et al. assessed the clinical response and side effects of F.S. and IPC in 118 children with IDA. All patients were given elemental iron 6 mg/kg/day in three divided doses. Patients who received F.S. had significantly higher hemoglobin and fewer residual complaints compared to those who received IPC. However, gastrointestinal side effects were more common with F.S. (7.6% versus 17%).<sup>68</sup> Sheikh et al. randomized 70 toddlers with IDA to receive F.S. or IPC at 6 mg/kg/day of elemental iron in three divided doses. Response and compliance with therapy were similar in both groups.<sup>69</sup> Mahmood et al randomized 170 children with IDA to receive F.S. or IPC at 6 mg/kg/day once daily for four weeks. Rise in hemoglobin was significantly higher in children treated with F.S. (87.1% versus 70.6%).<sup>70</sup> Powers et al randomized 80 infants and children aged 9 to 48 months with nutritional IDA to 3 mg/kg/day of elemental iron once daily for three months as either F.S. or IPC drops. The mean hemoglobin increased 1g/dL more in those who received F.S., and the proportion of children with complete resolution of IDA at the end of therapy was also significantly higher in the F.S. group (29% versus 6%). Both iron products were well-tolerated, but there were significantly more reports of diarrhea in the IPC group.<sup>71</sup> Mehta described a case series of patients from India who failed to respond to oral IPC therapy, while the same patients responded well to oral administration of ferrous fumarate.<sup>72</sup> Ruiz-Arguelles also showed that among 240 adults with IDA who received oral IPC, 31% failed to respond.<sup>73</sup> Yasa et al. randomized 103 children aged >6 months with IDA to IPC once daily or F.S. twice daily at 5 mg/kg/day. Efficacy was comparable, but IPC was associated with fewer gastrointestinal adverse events and better treatment acceptability.<sup>74</sup> Investigators from Greece randomized 100 children with iron deficiency or IDA to receive iron protein succinylate or IPC at 4 mg/kg/day elemental iron to a maximum daily dose of 80 mg for two months. Both drugs were well tolerated, but iron protein succinylate led to a faster hematologic response.<sup>75</sup> Cancelo-Hidalgo et al. performed a

systematic review of the tolerability of different iron supplements and found that ferrous fumarate had the highest rate of adverse events (47%) followed by F.S. and ferrous gluconate (32% and 30.9% respectively). Among all oral iron products, ferrous glycine sulfate, iron protein succinylate, and F.S. combined with mucoprotease were those better tolerated.<sup>76</sup> Regarding liposomal (sucrosomial) iron, a multicenter study of the Associazione Italiana Emato-Oncologia Pediatrica documented its excellent tolerance, i.e., the complete absence of gastrointestinal side effects, but the limited number of patients with mild IDA treated limits the conclusions that can be drawn regarding the clinical efficacy of this formulation in children.<sup>77</sup>

Based on the above-limited data, for infants and children with IDA we recommend therapy with oral F.S., 3 mg/kg in elemental iron, administered once daily (oral drops in infants, syrup in younger children, tablets in older ones).<sup>19</sup> Higher doses of F.S. up to 4-6 mg/kg/day in divided doses are unlikely to be more effective and are associated with more frequent gastrointestinal intolerance. If F.S. is not tolerated, IPC can be used (oral drops, syrup or tablets) at a daily dose of 3-5 mg/kg in one or two doses with meals,<sup>78</sup> but the response is slower compared to F.S. It is crucial to educate parents of children with IDA that for optimal absorption, F.S. should be given 30 minutes to two hours before or after meals with water or orange juice and that milk products should be avoided because they substantially decrease the absorption of elemental iron. IPC products can be used as an alternative in children who demonstrate gastrointestinal intolerance to F.S. Since the iron in IPC products is complex-bound, ionic interactions with food are unlikely,<sup>79</sup> and the medication can be ingested with a meal or shortly thereafter which is a practical advantage in infants. Iron protein succinylate and iron acetyl aspartylate, both available in single-dose potable vials of 80 mg, should be used in patients who cannot tolerate cheaper oral iron products. Finally, more studies of the innovative oral sucrosomial and the other liposomal oral iron products are required in order to document their efficacy in children with IDA.

The recommended duration of oral iron therapy is usually three months, but the duration should be adjusted to achieve normalization of hemoglobin, MCV, MCH, reticulocyte count, and serum ferritin. In addition, dietary modifications to address the underlying mechanisms of IDA are essential. More specifically, the amount of consumed milk should be limited to no more than 500 mL/day in toddlers, and rational consumption of meat products should be promoted.

**Parenteral Iron Therapy.** Intravenous iron completely bypasses the intestinal hepcidin-ferroportin pathway that regulates iron absorption but is

**Table 6.** Indications for intravenous iron therapy in children.

<ul style="list-style-type: none"><li>-Inability of the child to swallow oral iron products</li><li>-Failure of oral iron therapy (due to poor compliance or side effects)</li><li>-Inadequate iron absorption due to gastrointestinal diseases (e.g., untreated celiac disease, inflammatory bowel diseases, etc)</li><li>-Ongoing intestinal blood loss</li><li>-Need for rapid correction of IDA and patient's preference to avoid transfusion</li><li>-Functional IDA (e.g., chronic kidney disease, rheumatoid arthritis)</li></ul>
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infrequently used in children with IDA due to its high cost and the limited number of pediatric studies advocating its safety and efficacy. The first-generation parenteral iron products were high molecular weight iron dextrans that are not commercially available anymore due to the risk of severe anaphylactic reactions.<sup>80</sup> Low molecular weight iron dextran, ferric gluconate, and iron sucrose are second-generation intravenous iron products, with iron sucrose being the most widely used parenteral iron product worldwide. Unfortunately, it requires repeated intravenous administrations on alternate days if the estimated total body iron deficit is >200-300 mg.<sup>81</sup> Finally, three third-generation intravenous iron products became recently available, i.e., ferumoxytol, ferric carboxymaltose, and iron isomaltoside 1000. Although their use in children remains off-label, they can be used for total dose infusion, i.e., correction of the total iron deficit with a single infusion. **Table 6** summarizes indications for parenteral iron therapy in children with IDA. As shown,

failure of oral iron therapy, various gastrointestinal diseases, ongoing intestinal blood loss, the need for rapid anemia correction and functional iron deficiency or iron sequestration are valid indications for parenteral iron therapy in children.

**Conclusions.** IDA continues to affect a large number of children and women of childbearing age worldwide. Measures to prevent iron deficiency in developed countries should aim at specific populations at risk, since methods to increase iron intake in the general population may be unsafe for people affected with iron overload. In a setting with limited resources, further research is needed to clarify the physiological processes and mechanisms underlying the risks and benefits of supplemental iron for children exposed to parasitic infections, like malaria. In low-income countries, iron deficiency should not be addressed alone, but deficiencies of other micronutrients and hematinic factors, infections, and lead poisoning should be resolved, too<sup>82</sup>, and that will require measures to improve social and economic policies that fight poverty. Finally, physicians of various specialties treating patients with iron deficiency and IDA of diverse etiologies should familiarize themselves with the different causes of IDA and the several available therapeutic oral and parenteral iron products in order to better serve their patients.

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