Efficacy and Safety of Iron Administration in Juvenile Populations

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Abstract
Infantile iron deficiency anemia (IDA) reduces maximal lifetime cognitive capacity and can threaten the life of an adolescent mother in childbirth. Administration of iron is a component of strategies for preventing or reversing iron deficiency (ID) and iron can be given parenterally or as oral supplements or fortified food. Safety issues can arise at the point of administration, i.e. in the gut lumen, and as a consequence of excessive iron stores arising from the interventions. Recent improvements in the pharmacology of parenteral iron compounds open the way to greater consideration of the intravenous route in pediatric therapy, and even public health. Oral iron supplementation, usually with folic acid, is the main treatment of IDA in the clinical setting. It is often combined with multiple micronutrients and is also used for resolution of severe anemia at the community level and for prophylaxis in the nonanemic population. Fortification of staple food (such as flour), or age-specific foods (infant formula, complementary foods) and beverages are the usual methods for ID prophylaxis. Special iron-rich preparations (powders, crushable tablets, edible spreads) are available for home fortification. Biofortification, i.e. enriching the iron content of crops during cultivation, is a novel approach, yet to be fully implemented or evaluated for children. Side effects and toxicity after oral iron intake are seen in the gut lumen. After oral and parenteral iron intake, the rise in circulating iron can increase the risk of complications from coexisting infections, notably with malaria, and when individual iron status is adequate. Growth impairment occurs with exposure of iron-sufficient children to iron interventions, so that targeting of iron to ID individuals seems advisable. Numerous adverse consequences from accumulation of excessive total body iron stores show up as a consequence of iron-mediated oxidative stress. Incomplete maturation of iron homoeostasis may permit higher iron absorption before 6 months of age.

Introduction
Iron ions can oscillate between the divalent and trivalent status and, thus, participate in electron transfer. Evolution used this ability and incorporated iron in the prosthetic groups of a number of iron-dependent proteins, making it an essential element. Among the corresponding deficiency symptoms are anemia due to a lack of he-

Key Words
Iron administration · Public health · Food fortification · Dietary supplements · Parenteral iron
moglobin, impaired synthesis of ATP and proteins, and impaired metabolism of xenobiotic due to a lack of cytochromes, as well as compromised growth, tissue regeneration and cell-related immune defense due to a lack of DNA reductase [1]. At the same time, the ability of iron to transfer electrons can produce reactive oxygen species [2] with the potential to damage DNA, proteins and lipids. Efficacy and safety concerns are particularly relevant to pediatric populations in whom the timing to restore iron adequacy can be critical and safety of the recipient is the highest priority.

The section on nutritional aspects, i.e. on the possibilities to counter iron deficiency (ID), is arranged according to the different modes to supply extra iron at different age levels during growth and development. The section on iron-related safety concerns, in contrast, is arranged according to the accessibility and sensitivity of different compartments to excessive iron, including comments on maturation of the mechanisms of iron homoeostasis.

**Nutritional Aspects**

*Forms, Efficacy, Effectiveness and General Remarks*

Iron can be given by parenteral injection, through nutrient supplements, or through fortified foods and beverages by the enteral route. One can consider the ability of iron administration to reverse iron deficiency anemia (IDA) or to build reserves in iron storage sites under controlled, experimental conditions; this is a matter of efficacy. Once efficacy is established, the impact of interventions as part of the routine dietary or health systems becomes the measure of effectiveness.

For uptake from the intestinal lumen via the divalent metal transporter 1 (DMT1), iron in the intestinal lumen needs to be freely soluble and in the divalent state [3]. This is generally the case if oral iron supplements are taken on an empty stomach. In this situation, the efficacy of iron uptake is a function of dosage, insofar as DMT1 (luminal transport protein) and ferroportin (basolateral membrane transport protein) are both saturable [4]. Thus, fractional iron absorption decreases with increasing iron dosages. In absolute terms, however, more total iron will be taken up from a larger dose.

The conventional criteria for diagnosing anemia relevant to children are: 110 g/l, 0.5–5 years; 115 g/l, 5–12 years, and 120 g/l, 12–15 years [5]. These cutoff values are specific to sea level conditions, and an upward adjustment of the criteria must be made for populations living at high altitudes such as in La Paz, Bolivia. In the developing world, childhood anemia is primarily the result of dietary factors. In addition, blood-feeding parasites, such as hookworm, whipworm or schistosomes, are common causes of IDA in tropical settings after 4 years of age. Other pathological bleeding situations from benign causes, for example peptic disease and vascular malformations, to malignant causes, for example neoplastic tumors, can be the basis of childhood IDA in poor and affluent countries. Malabsorptive conditions, such as celiac disease, tropical enteropathy, and tropical sprue, may be the additional cause of the IDA. Hence, it is prudent in both low-income and affluent societies to conduct a diagnostic workup to exclude pathological bases for anemia while treating IDA with therapeutic doses of supplemental iron.

**Parenteral Iron Administration**

Therapeutic Iron Administration in Pediatric Practice

In recent years, a number of compounds for intravenous injection in clinical practice have come into use, which overcome the safety issues of iron dextran [6–9], and dosage schedules for their use in children are available.

Parenteral Iron Supplementation in Public Health

Intravenous iron replacement or prophylaxis in young children has not been widely explored in the era of the newer, intravenous compounds, such that no efficacy experiences can be cited. Until the recent changes in the pharmaceutical preparations of injectable iron, the risks of parenteral iron for prophylaxis in public health practice greatly outweighed the benefits [10]. The greater safety of new parenteral iron preparations and the logistical difficulties with consistent oral dosing may shift the risk/benefit ratio to a point where parenteral iron may become useful at the population level. An inherent limitation may be cost, as replacement injection with iron sucrose in Turkish adults averaged about 144 USD [11].

**Enteral Iron Supplementation**

Oral iron supplementation encompasses the administration of the nutrient in dosage forms such as capsules, tablets or elixirs. Iron can be given alone (single supplement), or along with other nutrients (multinutrient supplement). The most common companion nutrient is folic acid. A growing trend is to supplement iron as part of larger multinutrient combinations [12, 13].
Iron in Pediatric Practice

The motivation for supplementation can be either therapeutic or prophylactic. Therapeutic supplementation is generally intensive, 1–2 mg/kg/day [14], but of limited duration and directed at correcting IDA. Ideally, as part of practice, it can be accompanied by reliable measures of hematological status, both for the initial diagnosis and for monitoring of the red blood cell response.

Public Health Iron Supplementation

Prophylactic supplementation is aimed at building up or maintaining adequate iron reserves such that the iron needed for expansion of the erythrocyte pool will be available during growth. The internationally accepted threshold for intervention programs in infants and toddlers is when anemia prevalence in a specific segment of the population exceeds 40%, constituting a severe public health problem [5]. For infants and toddlers, aged 6–24 months, the recommended supplementation dose is 12.5 mg iron/day and 50 μg of folic acid [15], covering all members of the population group at risk. The efficacy of this recommendation has been confirmed in major field trials in Pemba Island, which is part of the Zanzibar archipelago of Tanzania [16], and in the lowlands of Nepal [17]. These trials, conducted in 2002 and 2003, used parallel protocols with 4 arms (placebo, zinc only, iron/folic acid only, and zinc + iron/folic acid) and involved a total of 33,000 infants and toddlers in the iron exposure groups across the 2 studies. The initial prevalence of anemia was well over 40% in both settings, so that 12.5 mg of iron/day and 50 μg of folic acid were supplemented for an interval of 12 months. Iron and hematological status was analyzed in a subgroup and clearly demonstrated that anemia rates at follow-up were lower than in placebo controls in both sites, confirming the efficacy of the international guidelines. Additional benefits, presumably attributable to the correction of ID, were uncovered in this series of guidelines. Additional benefits, presumably attributable to the correction of ID, were uncovered in this series of guidelines. Additional benefits, presumably attributable to the correction of ID, were uncovered in this series of guidelines. Additional benefits, presumably attributable to the correction of ID, were uncovered in this series of guidelines. Additional benefits, presumably attributable to the correction of ID, were uncovered in this series of guidelines. Additional benefits, presumably attributable to the correction of ID, were uncovered in this series of guidelines.

Guatemala has a unique national policy of supporting targeted iron supplementation on a weekly basis. It applies to 4 eligible segments of the society: young children, 6–60 months; nonpregnant adolescents, 15–19 years; pregnant women, and lactating mothers. This is based on the theoretical projections and proof-of-principle demonstrations by Viteri et al. [20] and Gross and colleagues [21]. In a large-scale, 4-nation multicenter trial, the International Research on Infant Supplementation Study [12], it was established that daily iron supplementation is more effective in a time-dependent manner than weekly dosing, but weekly dosing was significantly superior to placebo. In fact, weekly oral iron supplements reduced anemia in rural Cambodian schoolchildren [22]. Moreover, a systematic review of 55 trials suggests efficacy of iron supplementation for an iron-responsive change in hemoglobin among children under 6 years of age in nonmalarial areas on the order of 40–60% [23]. This review left the caveats that ‘the increase is greater in subjects who are anaemic at the start of the trial and lower in malarial hyperendemic areas and in those consuming iron-fortified food. The projected reductions in prevalence of anemia with iron supplementation alone highlight the need for additional area-specific interventions, particularly in malaria-prone regions’ [23].

Public health iron supplementation is poorly effective in pregnant women [24, 25], and in child programs evidence for effectiveness is sparse. Eden [26] recommends that, after breast-feeding or an iron-fortified formula is stopped, ID and IDA should be prevented by routine daily iron supplementation (10 mg iron/day) via iron-fortified vitamins, iron drops, or iron-fortified drinks. An extensive review of the literature reaching back to the 1970s failed to find conclusive effectiveness studies relating such iron supplementation to improved outcomes of anemia and ID prevention.

Food Fortification with Iron

Fortification is a prophylactic measure to reduce IDA prevalence in populations at risk. Iron-fortified foods provide more iron than would be consumed with that diet in its usual composition. Wheat flour and commercial bread are items commonly fortified with iron, and infant replacement formulas can both be unfortified and iron-fortified. The costs of food fortification are relatively minor as estimated both by the food additives industry [27] and public agencies [28].

When consumed with meals, iron binding to inhibitory food ligands, such as phytates and polyphenols, may impair its bioavailability considerably. Moreover, the more alkaline pH of the intestinal lumen favors the less bioavailable trivalent (ferric) oxidation state for added iron quantities. In addition, considerations of cost and oxidation of the food matrix have prompted the use of iron fortificants with a low inherent biological availabil-
ity. Ferrous sulfate, for instance, is effective and inexpensive, but can impart a metallic taste, discolor the food and contribute to accelerated spoilage [29].

Fortified Infant Formula

Recent studies in Mexico [30] and Bangladesh [31] demonstrate substantial anemia rates at 6 months for exclusively breast-fed children, which is earlier than considered in present recommendations. According to the model of best practices for early child feeding [32], introduction of adequate complementary feeding should only begin at 6 months. In parts of the world in which safe water is guaranteed, iron-fortified infant formulas and complementary food could provide iron support for the first semester of life.

Carefully controlled comparisons of iron-fortified formulas and nonfortified controls are legion in the literature, dating back to the 1970s. A recent study in a poor area of rural China by the Chinese Center for Disease Control confirmed these data and reported a better reduction of anemia prevalence and higher hematological values in infants fed an iron and multimicronutrient formula compared to an unfortified equivalent [33]. In some circumstances, ID in infants is prevented equally well by a formula with an iron concentration of below 2.5 mg/l as with doses of above 12 mg/l [34].

Iron-Fortified Complementary Foods

The WHO recommendations clearly call for the institution of ‘appropriate complementary feeding’ at 6 months of age [32]. Exclusive breast-feeding beyond 6 months is clearly a risk factor for ID [35, 36]. Even after 12 months of age, milk-based infant or follow-on formulas remain relevant to feeding. These are technically complementary foods as well. In the toddler years and beyond, iron-fortified formulas have been shown to be more effective in maintaining hemoglobin within the normal range than undiluted cow’s milk as the major nutritive beverage [37].

The earliest systematic investigation of iron-fortified complementary feeding has been performed in the last 20 years. A pioneering study from Santiago, Chile, revealed an equivalency of iron-fortified rice cereal with iron-fortified infant and toddler formula in virtually preventing anemia up to 15 months of age, as compared to unfortified cereals, for children weaned by 4 months [38]. Despite the title of this paper, this can be classified in its design as an efficacy study. In Swedish infants and toddlers, a complex relationship with iron intake was derived from studies in which either iron-fortified cereals or iron-fortified milk formulas were randomly assigned and both estimated iron intake and hematological variables were followed at 6-month landmarks [39].

Back in the 1970s, there were no conclusive data on the effectiveness of iron-fortified complementary foods to improve IDA and ID outcomes. Circumstantial evidence for effectiveness was derived from a temporal comparison within underprivileged families during the WIC (Women, Infants and Children) program in the late 1970s. The provision of iron-fortified infant formulas and cereals was associated with across-the-board improvement in hematological status [40]. Moreover, consumption of iron-fortified formula and >500 ml of cow’s milk per day were associated with a 22% increase and 25% decrease in ferritin, respectively, in 6- to 24-month-old New Zealanders [41]. The overall low prevalence of impaired iron status in this affluent population possibly limits the universality of these effectiveness findings to situations of more rampant ID and IDA. Also, daily servings of meals with an iron-fortified fish sauce reduced anemia in Cambodian schoolchildren [42]; iron citrate and NaFeEDTA were equally effective as fortificant compounds.

In summary, over the last 20 years, little has altered the validity of Dr. Peter Dallman’s 1990 prescription for preventing ID in the first 12 months of life: (1) maintaining breast-feeding for at least 6 months, if possible; (2) using an iron-fortified infant formula if a formula is used and using formula in preference to cow’s milk; (3) using iron-fortified infant cereal as one of the first solid foods, and (4) providing supplemental iron to low-birth-weight infants [43].

General Food Fortification

Foods of more general consumption are also relevant to the child population, in particular in the toddler and school years. Wheat flour is one of many examples that could be discussed. In 2008, a consortium of industry, academia and agencies met in Atlanta, Ga., USA, to develop international standards for the fortification of wheat and maize flours. A summary of recommendations evolving out of that experience appears in table 1 [44]. Biofortification is a new, largely untried, concept for fortifying foods at the level of the plant itself [45]. It can be done by adding iron-rich fertilizers to the soil or by genetic manipulation of the edible plant to retain more iron, or by presenting it in more bioavailable formats.
Home Fortification with Iron
In many parts of the world, the transition to home diet during the weaning process passes through grain-based gruels such as maize [46] or rice [13] porridge. Iron has been documented to be among the problem nutrients in most complementary feeding regimens [47]. In recent years, the notion of adding iron and other nutrients to complementary foods in the home, so-called home fortification, has advanced as a public health measure. The vehicles for home fortification include: (1) micronutrient powders in sachets (Sprinkles, MixMe), and (2) highly nutrient-dense spreads analogous to peanut butter [48]. The efficacy of iron in addressing ID from each of these home fortification modalities has been documented.

Safety Aspects

Supplementing highly bioavailable iron compounds can induce toxicity, the extent of which is modulated by the body’s state of iron repletion and the available antioxidant buffering capacity. Iannotti et al. [49] reviewed the randomized, placebo-controlled trials on the risks of iron supplementation in children and listed retarded growth, impaired cognitive, motor and behavioral development, increased susceptibility to diarrhea and malaria as safety concerns that affect primarily the juvenile population. Accordingly, iron was classified among the nutrients of highest risk by the German Federal Institute for Risk Assessment [50]. Here, we relate safety concerns of iron supplementation to their underlying origins (table 2).

Table 1. Criteria for food fortification

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<tr>
<td>1</td>
<td>Involve academia, government and industry, as well as consumers</td>
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<td>2</td>
<td>Provide scientific evidence of the intervention’s effectiveness</td>
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<td>and acceptability</td>
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<td>3</td>
<td>Assess food and micronutrient intakes in the target population</td>
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<td>4</td>
<td>Add adequate, yet safe, amounts of deficient micronutrients</td>
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<td>5</td>
<td>Use ingredients from a reliable source</td>
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<td>6</td>
<td>Monitor operational performance at production, sales point</td>
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<td></td>
<td>and household</td>
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<td>7</td>
<td>Strictly enforce regulations</td>
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Reproduced with permission from Bowley [44].

Table 2. Schematic considerations linking iron to safety issues in children: consequences of acute administration of or prolonged excessive exposure to iron by the anatomical or functional system

<table>
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<tr>
<th>Gastrointestinal tract</th>
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<tr>
<td>Direct irritation and erosion of mucosa</td>
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<td>Oxidation of the intraluminal contents and adjacent mucosa</td>
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<th>Vascular system</th>
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<td>Toxic cardiovascular shock</td>
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<td>Postprandial increases in non-transferrin-bound (‘free’) iron in circulation</td>
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<th>Central nervous system</th>
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<td>Reduced cognitive development</td>
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<th>Endocrine-nutritional growth axis</th>
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<td>Impaired linear and ponderal growth</td>
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Note 1: Thought to be involved in the increased virulence of malaria in iron-adequate children [16].

Intestinal Lumen

The iron-related mucosal irritation and oxidative damage in the intestinal lumen are proportional to luminal iron concentrations [51]. Intake of 10–20 mg iron/kg body weight is regarded as a no-observed-adverse-effect level for iron-induced erosions in the gastrointestinal tract leading to diarrhea with massive blood losses and finally to scarring of the gastrointestinal tract [52]. Iron dosages of 50–60 mg iron/kg body weight can cause nausea, vomiting, epigastric discomfort and altered gastrointestinal motility in adults. The concentration of thiobarbituric acid-reactive substances and the Trolox-equivalent antioxidant capacity increased 30 min after duodenal gavage of 80 mg iron in adult volunteers [53]. In healthy adult volunteers, intake of 19 mg iron/day, which is in the recommended daily allowance dose range for adult women, significantly increased luminal reactive oxygen species production [54].

Interfering Influences in the Intestinal Lumen

Diets rich in phytate and polyphenols reduce iron availability, but also the toxic potential of iron in the gut lumen. Thus, iron-binding phytate protected pig colon from lipid peroxidation [55]. αs-Casein, casein phosphopeptides and phosphoserine residues in cow’s milk seem to have similar iron-binding properties [56]. Helicobacter pylori infections are often observed in children of low socioeconomic status, and frequently lead to hypochloremia [57] compromising iron bioavailability [58] and reducing the gastric barrier against pathogens [59], which increases the incidence of diarrhea [23, 60].
**Vascular System**

Along with cost issues, the risk of spreading HIV and hepatitis viruses argue strongly against routine use of parenteral iron preparations in Third World public health settings [10]. Large amounts of absorbed iron cause cardiovascular shock due to capillary leakage and arteriolar dilatation [61, 62], showing that the mucosa is not a reliable barrier against high iron doses. Young children are at particular risk, as iron toxicity shows a clear dose-response relationship as related to body weight [61].

Non-transferrin-bound iron (NTBI) may induce oxidative stress in the vascular endothelium [63], and, thus, participate in the pathogenesis of malaria. The Pema trial [16] revealed a correlation between the intake of iron supplements and the clinical course of *Falciparum* malaria at dosages (12.5 mg iron/day, infants 1–35 months of age) recommended by the UN Agencies [15]. The incidence of hospital admissions (11%) and death cases (15%) due to hepatic and cerebral complications of malaria was significantly higher in iron-supplemented as compared to nonsupplemented infants. It was suggested that NTBI may facilitate the attachment of plasmodia to the vascular endothelium and the subsequent penetration through vascular walls [64]. A putative mechanism is via ICAM-1 receptors [65]. NTBI increases after absorption of pharmaceutical iron compounds [66, 67] and remains high for longer periods in well iron-replete individuals [68], leading to more serious clinical malaria courses in iron-replete than in iron-deficient persons in a subgroup of the Pemba trial [16].

**Iron Effects in the Tissues**

Iron is essential for the development, myelinization, monoamine synthesis and energy metabolism in central nervous system glial cells and neurons [69]. Its deficiency seems to impair the development of cognitive function and behavioral performance in animals and humans that may not be fully restorable [69, 70]. Other nutritional deficiencies and socioeconomic factors may be confounding [70, 71], so that iron supplementation had but a modest positive effect on mental development in a systematic review analysis [72]. Excessive iron may even be detrimental for central nervous system functions in later years. Thus, cognitive, intellectual, and mental development at 10 years of age showed lower scores in children who had received high-iron milk-based formula as compared to lower fortification levels (12 mg iron/l vs. 2.3 mg iron/l) at 6–12 months of age [73].

Impaired growth as a consequence of iron supplementation has been repeatedly observed in iron-adequate children [74–77]. It has been speculated that iron itself, iron-mediated oxidative stress that can damage unsaturated fatty acids and DNA [78, 79], or an antagonistic effect of iron on zinc metabolism, may be the underlying cause of growth impairment. The latter might occur via zinc interaction with insulin-like growth hormone factor [80]. In addition, iron-related systemic inflammation induces catabolic reactions [81], which have also been suggested to cause growth retardation [82].

Iron supplementation may, indeed, cause oxidative stress. Thus, 60 mg iron/day increased thiobarbituric acid-reactive substances in pregnant women [83], breath alkanes in human adults increased after a single dose of 10 mg iron [84] and supplementation of 20 mg iron/day increased the acute-phase protein, α1-antichymotrypsin, in Guatemalan children [85]. Additional field research points in the same direction. Offering oral iron and folic acid twice weekly (approx. 1 recommended daily allowance/day) to Cambodian infants increased the prevalence of fatigue, diarrhea, and upper respiratory infections as compared to controls [13]. Simultaneous co-administration of selenium, zinc, copper, iodine, and vitamins A, B2, B6, B12, C, and D reduced the prevalence of these symptoms to a lower level than in the placebo group [13]. Due to a diet low in antioxidant micronutrients (e.g. vitamins A and E, selenium, zinc), the iron-related damage was proposed to be accentuated by a compromised antioxidant capacity in this population.

The lack of iron-induced growth impairment in ID suggests that its pathophysiology seems to be related to the lower amounts of iron channeled into erythropoiesis and stores in iron-replete children [86, 87]. To avoid negative side effects, such as severe courses of *Falciparum* malaria and growth retardation, iron supplementation should, therefore, be targeted only to iron-deficient children. Because of the risk of spreading blood-borne diseases and the considerable effort and cost of full characterization of individual iron status in blood samples, noninvasive methods (inoffensive, laser-based skin probes) to determine hemoglobin concentrations are presently being tested [88]. Their response to iron supplementation can help to assess IDA noninvasively in children >6 months of age, which may offer a way out of the iron supplementation dilemma in malarial zones.

**Maturation of Iron Homoeostasis**

Between 4 and 6 months of age, iron supplementation increased hemoglobin and serum ferritin concentrations to the same extent in iron-deficient Honduran infants as in their iron-adequate Swedish counterparts, whereas at
an age of 6–9 months increments were higher in ID. Intestinal barrier function, thus, seems to be impaired in the iron-adequate infants of the younger age bracket [89]. Accordingly, studies in suckling rats revealed a nonfunctional intracellular localization of the iron transport proteins DMT1 and ferroportin in mid infancy (10 days of age in the rat). In older rat pups (20 days of age), by contrast, both transporters were appropriately localized in the apical and basolateral membranes, respectively [80]. Along with a parallel rat study that showed no adequate response of intestinal DMT1 and ferroportin expression before day 20 [90], these findings suggest impaired regulation of intestinal iron transport in early infancy, which is supported by studies in mouse pups [91]. Toddlers, in contrast, absorb iron in close correlation to iron losses [92], showing that the mechanisms of iron homeostasis at this age are mature and operational. However, iron losses in toddlers are significantly higher than in adults, which may be due to a higher turnover of mucosal shedding or to intestinal blood losses after high consumption of cow’s milk [93].

In infants, pharmaceutical iron supplements seem to be stored in ferritin, whereas iron offered with fortified foods seems to be utilized primarily in erythropoiesis. Such different targeting was proposed to depend on the much faster absorption rates for pharmaceutical iron preparations. They cause significant postabsorptive peaks in serum iron concentrations, which may induce a marked hepcidin response and, thus, divert iron primarily to the ferritin stores in the reticuloendothelial system. Such postabsorptive serum iron peaks should be much less marked after food iron intake [94].

**Conclusion**

Iron is truly a two-edged sword: on the one hand, an essential nutrient, indispensable for oxygen transport, oxidation reduction chemistry and cellular defense; on the other hand, a potent oxidant and irritant, which damages tissues, impairs growth and interacts with human pathogens, increasing their virulence in states of excess. For pediatrics and juvenile public health, a full understanding of the issues that make iron administration efficacious and effective, while at the same time safe in the short and long term, is essential for the well-being of patients and the population at large.

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