European Journal of Pediatrics
https://doi.org/10.1007/s00431-020-03597-5

REVIEW

Diagnosis and management of iron deficiency in children with or without anemia: consensus recommendations of the SPOG Pediatric Hematology Working Group

Veneranda Mattiello[1] · Markus Schmugge[2] · Heinz Hengartner[3] · Nicolas von der Weid[4] · Raffaele Renella[5] · on behalf of the SPOG Pediatric Hematology Working Group

Received: 18 December 2019 / Revised: 22 January 2020 / Accepted: 27 January 2020

Abstract

Iron deficiency is the most prevalent nutritional deficiency affecting children and adolescents worldwide. A consistent body of epidemiological data demonstrates an increased incidence of iron deficiency at three timepoints: in the neonatal period, in preschool children, and in adolescents, where it particularly affects females.

Conclusion: This narrative review focuses on the most suggestive symptoms of iron deficiency in childhood, describes the diagnostic procedures in situations with or without anemia, and provides Swiss expert-based management recommendations for the pediatric context.

What is Known:
- *Iron deficiency (ID) is one of the most common challenges faced by pediatricians.*
- *Significant progress in the diagnosis and therapy of ID has been made over the last decade.*

What is New:
- *Our expert panel provides ID management recommendations based on the best available evidence.*
- *They include strategies for ID diagnosis and therapy, both oral and intravenous.*

Keywords Iron deficiency · Children · Anemia · Oral iron therapy · Intravenous iron therapy

Veneranda Mattiello and Markus Schmugge contributed equally to the manuscript.

Communicated by Peter de Winter

✉ Raffaele Renella
Raffaele.Renella@chuv.ch

[1] Department "Woman-Mother-Child and Adolescent", Pediatric Hematology-Oncology Unit, Division of Pediatrics, University Hospital of Geneva, Geneva, Switzerland

[2] Division of Pediatric Hematology, University Children's Hospital of Zurich, Zurich, Switzerland

[3] Pediatric Hematology-Oncology Unit, Children's Hospital of Sankt Gallen, Sankt Gallen, Switzerland

[4] Pediatric Hematology-Oncology Department, University Children's Hospital and University of Basel, Basel, Switzerland

[5] Department "Woman-Mother-Child", Pediatric Hematology-Oncology Unit, Division of Pediatrics, Lausanne University Hospital and University of Lausanne, Vaudois, BH11, Rue du Bugnon 46, 1011 Lausanne, Switzerland

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ATP	Adenosine triphosphate
BHS	Breath-holding spells
CHr	Reticulocyte hemoglobin content
Hb	Hemoglobin
IBD	Inflammatory bowel disease
ID	Iron deficiency
IDA	Iron deficiency with anemia
IDWA	Iron deficiency without anemia
IRIDA	Iron refractory iron deficiency anemia
IRLSSG	International Restless Legs Syndrome Study Group
IUGR	Intra-uterine growth retardation
IV	Intravenous
LS	List of specialties (Swiss-approved medicines, FDA/EMA equivalent)
MCV	Mean corpuscular volume
MCH	Mean corpuscular/cellular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration

Published online: 04 February 2020

NHANES	National health and nutrition examination survey
PLMD	Periodic limb movement disorder
RBC	Red blood cells
RDW	Red cell distribution width
RET-He	Reticulocyte hemoglobin content
RLS	Restless legs syndrome
SF	Serum ferritin
SPOG	Swiss Pediatric Oncology Group
sTfR	Serum soluble transferrin receptor
URIDA	Unexplained refractory iron deficiency anemia
WHO	World Health Organization
ZnPP	Zinc protoporphyrin

Background and introduction

Iron deficiency (ID) is one of the most common challenges faced by pediatricians. While the majority of cases are straightforward in both diagnosis and management, significant progress on the phenotype of ID, its diagnosis, and therapy has been made over the last decade. Therefore, we felt a concise update for general practice to be necessary, as well as clinically applicable recommendations aiming to increase quality of care. Thus, we formed a panel of five practicing Swiss pediatric hematologists delegated by the Hematology Working Group of the Swiss Pediatric Oncology Group clinical trial organization (www.spog.ch) and met in person over the last 2 years to identify, review, and interpret any available data on the diagnosis and therapy of ID in children (age 0 to 18 years old) with or without anemia. The US National Library of Medicine/MEDLINE database was searched for articles or letters published in full-length without strict limitation of the publication date, and reports were collected by the authors according to relevance. Reports published in English, French, German, and Italian were included, while documents in other languages were not considered, due to the impossibility to integrate content appropriately. Reports were read by the panel of experts and discussed at face-to-face meetings, prior to generation of summaries of content and evidence. Consensus was found on each of the main topics outlined in this review.

Epidemiology

ID is the most widespread nutritional deficiency affecting more than 2 billion of people worldwide according to the World Health Organization (WHO) [1]. While the prevalence of ID among children and adolescents in Switzerland is not known, the U.S. National Health and Nutrition Examination Survey (NHANES-IV) observed that 7% of infants aged 1–2 years and 9% of adolescent girls have ID without anemia (IDWA) [2]. In populations with comparable socio-economic and ethnic background, prevalence is estimated between 2 and 6% of preschool children and between 8 and 20% of female adolescents [3, 4]. Many authors have reported the relationship of socio-economical status (i.e., poverty), education levels (i.e., lower), and ID [5]. In a recently published comprehensive study on the global burden of disease in children and adolescents, ID was the leading cause of years lived with disability, affecting more than 600 million individuals in 2013 [6].

Symptoms and clinical signs of iron deficiency with or without anemia

A number of symptoms can be associated to iron deficiency (ID) with (IDA) or without anemia (IDWA), as shown in Table 1. Such symptoms become suggestive for the diagnosis of ID or IDA in the context of the patient's history and/or additional laboratory findings only. Clinical manifestations depend on age, the presence and severity of anemia, co-morbidities, and rate of onset [5]. Of course, a broad differential diagnosis exists for these rather aspecific symptoms, as they may represent multifactorial processes, may be linked to

Table 1 Symptoms and clinical signs of iron deficiency with or without anemia

Symptoms and clinical signs of iron deficiency (with or without anemia)
Angular cheilitis
Koilonychia/spoon nails
Hair loss, dry, and damaged hair
Dry and rough skin
Glossitis/decreased papillation of the tongue/burning tongue
Plummer-Vinson syndrome/esophageal and pharyngeal webs
Dysphagia
Loss of appetite
Dysgeusia
Pica
Fatigue
Behavioral changes
Attention deficit/hyperactivity disorder
Restless legs syndrome
Sensitivity to cold
Sleep disorders
Irritability/malaise
Breath-holding spell
Symptoms and clinical signs of anemia
Dyspnea on exertion
Pallor
Palpitations
Headaches
Tinnitus
Vertigo
Cardiac murmur
Tachycardia
Angina pectoris
Hemodynamic instability
Heart failure
Syncope
Stroke

global poor nutrition or associated to other underlying conditions (i.e., malabsorption, renal disease, rheumatic/inflammatory conditions). Unexplained fatigue, for example, is the most common symptom of ID, with or without anemia, but may be associated with a number of confounding clinical conditions [7]. Weakness, pallor, irritability, and lightheadedness are often observed in children with both IDA and/or IDWA. Severe symptoms like tachypnea, palpitations, and vertigo are usually observed only in anemic patients. A long-standing ID can also lead to an alteration of epithelial cells such as dry mouth, cheilitis, atrophic glossitis, or hair loss. In rare cases, esophageal membranes (Plummer-Vinson syndrome) may appear [8]. Neurological symptoms have also been observed in children with ID such as attention-deficit/hyperactivity disorder (ADHD) or restless legs syndrome, and their attribution to ID itself remains controversial. In this review, we would like to focus on some of the most suggestive symptoms of ID in childhood, without discussing the more common features of anemia.

Psychomotor and developmental signs and symptoms

Iron plays a crucial role in the cognitive development of children and adolescents. Experimental animal models have shown that ID before birth or in the first months of life interferes with several neurodevelopmental processes such as myelination, dendritogenesis, synaptogenesis, neurotransmission, and neurometabolism [9, 10]. In children, ID can therefore lead to delayed cognitive, motor, attention and memory deficits, visual and auditory deficits, decreased school performance, and/or behavioral disorders, some with persistent long-term effects [9–11]. Current scientific evidence suggests that the age of onset together with the duration and severity of ID, as well as the presence of anemia, could affect cognitive and neurophysiological outcomes in childhood [12]. Age, presence, and severity of anemia and duration of treatment have been highlighted as possible determinants for efficacy of iron substitution, but the effects on correcting these symptoms, however, remain under debate. For infants and young children under 2 years of age, there is currently no clear scientific evidence for a beneficial effect of iron supplementation on cognition. These results are confirmed by systematic reviews of the literature and recent meta-analyses [13, 14]. On the other hand, many authors report an improvement in motor performance after iron substitution, although this remains controversial [15–22]. Among preschool children (2 to 5 years old) with ID, modest but significant results are observed after substitution, but only in anemic children, particularly in terms of language as well as visual and selective attention. These results are summarized in a recent meta-analysis [23]. Anemic children over 7 years of age with severe ID and following long lasting iron treatment seem to have the better outcomes [24]. However, even in those older children, no efficacy in terms of improvement of memory or motor development was noted. In adolescents and young women of childbearing age, ID can also lead to decreased psychomotor skills and concentration, mainly due to anemia with an impact on school performance [25, 26]. In this age group, iron substitution is effective in improving attention, concentration and verbal learning [23, 27].

Neurologic disorders

Iron substitution has demonstrated some benefit in other neurologic conditions in young children, including breath-holding spells and restless legs syndrome. Evidence is limited to case series, but oral iron supplementation for such patients with IDWA could be beneficial while presenting limited risk of harm and could potentially be discussed on an individual case basis.

Attention-deficit/hyperactivity disorder

ADHD is the most common behavioral disorder in children. The diagnosis of ADHD should be considered in children 4 years or older with poor attention, distractibility, hyperactivity, impulsiveness, impaired academic performance, or behavioral problems at home or at school [28]. A link between ID and ADHD has been suggested by several authors [29–36], while others do not find any disruption of the iron balance in this population [37]. Firstly, significantly lower serum ferritin levels have been observed in children with ADHD when compared to healthy controls [38]. Furthermore, iron substitution apparently leads to an improvement of ADHD symptoms in children with low serum ferritin levels [29, 39]. Moreover, ID has been postulated to cause a dysregulation of central dopaminergic neurotransmission, which may play an important role in the pathophysiology of ADHD [40]. However, the exact role of ID in ADHD remains to be confirmed. Concerning the efficacy of iron substitution on ADHD symptoms, improvements in hyperactivity were recently reported after a combined zinc iron substitution in a small series of children with ADHD with zinc and iron deficiencies [41]. These results are consistent with previous reports [29, 39]. However, those studies were conducted in small cohorts, present many confounders, and need to be confirmed in larger populations. In conclusion, universal iron substitution in patients ADHD is not recommended but a potential beneficial effect in iron deficient children with ADHD is not excluded.

Restless legs syndrome

ID has been implicated in the pathogenesis of restless legs syndrome (RLS), a relatively common neurological disorder (1.7–1.9% in school-aged children and 2–3.6% in adolescents), which significantly impacts quality of life [42, 43].

RLS is a movement disorder characterized by an often unpleasant or uncomfortable urge to move the legs that occurs during periods of inactivity or sleep. Clinical and consensus diagnostic criteria for RLS have been updated in 2013 [44]. A role for the central dopaminergic system in the genesis of RLS has been suggested by the efficacy of dopaminergic agonists in its therapy, even if the physiopathology remains poorly understood. A further link between disturbance of dopaminergic neurotransmission in the striatum and iron metabolism is suggested by animal models. Decreased brain iron has been documented in this condition by histologic, radiological, and cerebrospinal fluid analyses and seems to lead to hypoxia and myelin loss as well as dopaminergic system abnormalities [44, 45]. Moreover genome-wide association studies identified several genetic variants predisposing to RLS. Two of them (MEIS1 and BTBD9) appear to influence expression of periodic limb movements of sleep as well as iron homeostasis. This correlation is consistent with the suspected involvement of iron depletion in the pathogenesis of RLS [46, 47]. Considering the current scientific evidence, the 2018 consensus RLS treatment guidelines recommend iron substitution in children with RLS if ferritin level is below 50 mcg/L [48].

Breath-holding spells

Another neurologic condition potentially associated with ID is breath-holding spells (BHS). BHS is a benign paroxysmal non-epileptic disorder occurring in otherwise healthy children 6 to 48 months of age. Several studies suggest an association between BHS and anemia [49]. ID seems to increase frequency of BHS attacks. Iron substitution could lead to a decrease in the frequency and intensity of seizures in children with BHS, regardless of their iron status suggesting an iron imbalance role in the development of this disorder [50]. A possible causative role of ID could be attributed to increased activity of serotonin and/or increased availability of sympathomimetic neurotransmitters due to a reduction of degrading enzymes [51, 52]. In fact, even if the pathophysiology of BHS remains unclear, autonomic nervous system dysfunction appears to play a role in its development [52].

Pica

Pica is an eating disorder characterized by the desire for and ingestion of non-food materials (clay, soil, paper, laundry starch, etc.) [53]. It is observed more frequently in children and adult women [54]. Pica is described in many clinical settings and differentiated from pagophagia (craving for ice). It is not considered specific for ID and tends to occur mostly in the setting of severe ID. However, pagophagia is considered quite specific to ID and responds quickly to iron substitution [55]. Pica can also contribute to ID by reducing gut iron absorption, depending on the substance ingested. The exact physiopathology of pica associated with ID is not yet elucidated; however, a decrease in the enzymatic activity of cyclooxygenase has been reported [56].

Iron and physical performance

Several authors have described an increased prevalence of ID among physically active people compared to non-athletic controls [57]. Physical activity and in particular regular aerobic exercise can lead to ID through different mechanisms. First, among athletes, there is an increase of iron losses via sweating, the gastrointestinal system, and the urinary tract (mainly related to hypoxia, increased blood pressure, acidosis, etc.). Second, exercise-induced hemolysis can typically be observed in runners, although it has also been described in swimmers, rowers, or bikers [58]. Clinically, it is often difficult to differentiate exercise-induced rhabdomyolysis from hemolysis, which is rarer, and specific tests for myolysis should be performed in settings warranting it. Third, exercise-induced inflammation has also recently been pointed out as potential cause of reduced iron absorption, probably related to an increase in hepcidin secretion induced by physical activity [59, 60]. Finally, an increase in exercise-related nutritional needs is present in athletes [61, 62].

In parallel, a decrease in physical performance has been reported in adolescents with IDA or IDWA, especially in endurance activities [63]. Indeed, athletic performance is influenced by aerobic capacity and iron is involved in various oxidative reactions leading to adenosine triphosphate (ATP) production. In a study of college rowers, athletes with IDWA displayed inferior physical performance and energy efficiency compared to non-ID athletes [58, 62]. It has to be stressed that to our knowledge, there is no literature on the effect of iron supplementation on the athletic performance in non-anemic children below the age of 13 years. There is a greater improvement in endurance in aerobic exercise among young women runners compared to unsubstituted athletes [57, 64]. A decrease in muscle fatigability was also observed in a cohort of young sedentary women after substitution [65]. The effects of substitution are seen mainly in the presence of severe ID [66]. Effect on oxygen consumption (maximum VO_2 or VO_{2max}) after substitution has been demonstrated only in anemic subjects. This parameter, being dependent on the delivery of oxygen to tissues, is improved proportionally to the increase in hemoglobin levels [57]. A recent meta-analysis confirms an improvement in endurance activities in non-anemic athletes after iron substitution in presence of severe ID (defined by ferritin level < 20 mcg/L). In conclusion, there is currently not clear scientific evidence supporting iron substitution in athletes in the pediatric age-range with normal hemoglobin and ferritin levels.

Iron and the immune system

ID leads in vitro to an inhibition of maturation, proliferation, and activation of lymphocytes with impairment of cell-mediated immunity, and iron is a known co-factor in the synthesis of myeloperoxidase and nitric oxide synthase, which are implicated in the eradication of infectious pathogens [11]. The clinical consequences of these abnormalities on the risk of infection in children and the effect of iron substitution are currently unclear [67]. Some authors report of an increased risk of reactivation of latent infections like malaria, brucellosis, or tuberculosis [68]. A systematic study focusing on children demonstrated no effect (either reduction or increase) in the number of infectious events following iron replacement treatments [69]. Further randomized controlled studies focusing on children with ID are needed to clarify the direct causality of ID or the benefit of iron substitution a child's susceptibility to infection.

"Red flags" for iron deficiency with anemia

IDA-related symptoms usually have a gradual onset, and children are frequently asymptomatic. Nevertheless, if the anemia is severe, signs of severity ("red flags") can appear, such as dyspnea, palpitations, vertigo, tachycardia, syncope leading potentially to hemodynamic instability, myocardial infarction, heart failure, or stroke. If any of these symptoms occur, the patient will need urgent medical attention and detailed evaluation in order to exclude other causes or co-morbidities, as well as optimal specific care with appropriate hemodynamic support and potentially transfusion. The abovementioned symptoms are not specific of IDA and can be noticed in others forms of anemia. Therefore, in the clinical assessment of children with anemia, pediatricians must be careful about the presence of associated signs and symptoms, suggesting a differential diagnosis that could require urgent medical attention. These include:

- Jaundice ± splenomegaly suggesting hemolytic anemia
- Bleeding signs (ecchymoses and/or petechiae, hematuria, rectorrhagia, epistaxis) suggesting a bone marrow involvement, coagulopathy, or auto-immune condition
- Fever of unknown origin, recent weight loss (especially if unexplained/undesired > 10%), night sweats, hepatosplenomegaly, and/or lymphadenopathy suggesting an oncological condition
- Additional laboratory abnormalities (i.e., thrombocytopenia, neutropenia, "bicytopenia")

Risk factors for iron deficiency

Many epidemiological studies have shown an increased prevalence of ID in children at three time points: the neonatal period, in preschool children, and in adolescents (especially females) [23, 70]. In the neonatal period, the risk of ID is increased after prematurity or intrauterine growth retardation. It can be found when the initiation of solid foods ideally occurring at 6–9 months of age is delayed [71]. The etiology of ID in children and adolescents varies according to age and sex (Table 2) and is mainly due to three key mechanisms: inadequate intake, malabsorption, and blood loss [72, 73]. In children and adolescents, ID is mostly due to increased iron needs related to growth and development (functional or physiologic ID). Healthy children and adolescents may also be at risk of ID because of diet restrictions (vegetarians, vegans) or elite endurance activities (as discussed above) [74]. Although less frequent in the pediatric population compared to adults, we have to mention ID related to chronic inflammatory conditions (observed in oncological disorders, inflammatory bowel disease [IBD], chronic renal failure, and other chronic inflammatory diseases). Another very rare condition generally observed in < 1:1,000,000 individuals in the general population is genetic/inherited ID. The latter condition is usually associated with a moderate microcytic hypochromic anemia, occurring after the postnatal period: IRIDA (iron refractory iron deficiency anemia). IRIDA is an autosomal recessive disease caused by mutations in the transmembrane serine protease 6 gene (TMPRSS6) encoding matriptase-2 (MT-2) [75]. This protease is responsible for the negative regulation of hepcidin, the main regulator of ferric homeostasis. Hepcidin is a polypeptide secreted at the hepatic level, which induces endocytosis and degradation of ferroportin (a transmembrane iron transporter located at the basement membrane of enterocytes, macrophages and hepatocytes), thus decreasing plasma transfer of iron and its concentration [70, 76]. In IRIDA, patients are unable to respond to ID by suppressing hepcidin expression and are refractory to oral iron substitution displaying a partial response to intravenous treatment [75]. Studies are currently ongoing, aiming to identify new molecular alterations in enzymes related to iron metabolism that potentially could lead to iron deficiency anemia. [77]

Diagnosis of iron deficiency with or without anemia

Testing for iron deficiency

The diagnosis of IDA/IDWA requires laboratory testing [74, 78]. We recommend testing for ID in presence of symptoms suggestive of anemia or iron deficiency (as summarized in Table 1). The American Academy of Pediatrics suggests a routine screening for IDA for all children at the age of 12 months by using hemoglobin (Hb) concentration [79]. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and other European and North

Table 2 Etiology of iron deficiency in children and adolescents according to age

Age	Etiology			
	Insufficient supply	Malabsorption	Blood loss	Others
Newborn	Maternal IDA Maternal diabetes Pre-eclampsia Chronic maternal disease Maternal smoking Gestational age (prematurity) Parity, gemellarity IUGR Early cord clamping Peripartum hemorrhage	Intestinal malrotation/volvulus Digestive surgery	Hemolysis Blood withdrawals Necrotizing enterocolitis Intestinal malrotation/volvulus	Erythropoiesis stimulating agents Genetics
Infant (6–12 months)	Exclusive breastfeeding > 6 months Early introduction of cow's milk (before 1 year of age)	Volvulus Digestive surgery *Helicobacter pylori* Celiac disease	Bovine protein allergy Volvulus Invagination	Genetics
Children (1–4 years)	Low/insufficient iron intake Diet related	Celiac disease Volvulus Short bowel syndrome Food intolerances *Helicobacter pylori*	Eosinophilic gastroenteritis Esophagitis Meckel's diverticulum Volvulus invagination Parasitic infections Polyps Angiomas Hemolysis Hereditary hemorrhagic telangiectasia	Drugs Genetics
Children (5–12 years)	Vegetarianism/veganism Eating disorder	Celiac disease Volvulus Short-bowel syndrome Atrophic gastritis *Helicobacter pylori*	Meckel's diverticulum Parasitic infections Polyps Angiomas Hemolysis Hereditary hemorrhagic telangiectasia Idiopathic pulmonary hemosiderosis Kidney/immunologic/rheumatologic diseases	Drugs Genetics
Adolescents	Vegetarianism Eating disorder	Celiac disease Short-bowel syndrome Atrophic gastritis *Helicobacter pylori*	Heavy menses Chronic inflammatory bowel diseases Parasitic infection Esophagitis Polyps Angiomas Hemolysis Hemorrhagic telangiectasia Kidney/rheumatological/immunological diseases	Elite endurance activities Drugs Genetics

American societies do not recommend universal laboratory screening for IDA in young children, citing lack of direct evidence of the benefits or harms of such approach [3, 80, 81]. Nevertheless, all experts agree that a screening is recommended in children and adolescents with signs and symptoms, as listed in Table 1. The initial blood testing can be capillary and must include Hb, red blood cells (RBC), hematocrit, white blood cells, platelets, as well as RBC indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration MCHC]), RDW, reticulocyte count, and ferritin (Tables 3 and 4).

- Hb: Hb levels will show the presence of anemia. Anemia is defined by a reduced Hb value 5th percentile below the normal hemoglobin value specified for that age [2].
- RBC indices: ID is defined by a decreased MCV, MCHC, and MCH, with well-validated standards and little variation by age. A decrease in MCHC is frequently seen first in ID. However, these are late and non-specific markers of ID while a decrease in MCV is also observed in children with thalassemia or inflammatory anemia [2, 82].
- RDW (red cell distribution width) provides the statistical analysis of the standard deviation of the MCV. In ID and IDA, the RDW is increased.
- Ferritin: Serum ferritin (SF) is the most specific marker for the diagnosis of ID, as its concentration is proportional to the body's total iron stores [11, 76]. It is also the earliest marker of ID. It is an inexpensive test and can be performed with a very small amount of blood from a capillary sample. Although many studies and most laboratories usually define a decreased SF at levels below 12–40 μg/L in the general population [83], intervals used in clinical trials have not been standardized [11, 84]. In addition, SF levels vary with age. WHO defines ID as SF < 12 mcg/L in children under 5 years of age and < 15 mcg/L in individuals over 5 years of age [85]. For children aged 1 to 3 years, the American Academy of Pediatrics recommends a threshold value of SF < 10–12 mcg/L for the definition of ID [79]. Interpretation of SF levels in infants < 12 months is difficult as distinct normal values exist for the first 6 months and are higher compared to older children, but thresholds for ID are not well established in this age group. Some authors recently suggested that the diagnostic accuracy of SF could be improved in young children by increasing the cutoff to 18–24 mcg/L [86–89]. Previous studies found significant differences according to the SF measurement assay, making the comparison of SF results from different laboratories very complex [90, 91]. Finally, interpretation of SF levels can be difficult in cases of concomitant acute or chronic inflammatory conditions as SF is an acute phase reactant and may be increased for weeks during and after infection and inflammation [74]. Additionally, the concentration of SF increases after exercise and can remain high for several days after maximum effort [61].
- In situations where an inflammatory state or an infection is clinically suspected upfront, C-reactive protein (CRP)/erythrocytes sedimentation rate (ESR), in order to exclude possible confounding modifiers of SF level measurements.

Table 3 Normal ranges for Hb, MCV, Ferritin (Children's Hospital, Zurich, Switzerland)

Age	Hemoglobin (g/L)	MCV (fl)	Ferritin (μg/L)
0–7 days	135–200	95–115	153–1092
8–30 days	100–160	85–100	247–692
1–3 months	95–145	85–100	148–744
4–9 months	95–135	75–95	21–240
9–24 months	105–135	75–85	10–168
2–16 years	115–150	77–85	10–99
> 16 years (females)	120–160	78–95	18–103
> 16 years (males)	130–170	78–95	16–213

Supplementary (second-line) testing

Additional diagnostic testing is seldom necessary in order to better assess the presence and severity of ID in general pediatric practice, but here are some frequently ordered assays:

- Serum iron concentration, total iron binding capacity, transferrin saturation: In cases of ID, serum iron is reduced, and total iron-binding capacity is increased, resulting in a substantial reduction in transferrin saturation (i.e., the ratio of serum iron to total iron-binding capacity). The threshold of 16% of transferrin saturation is generally used to screen for ID, but there are age-specific variations [5, 92]. These markers are, as SF, acute phase reactants and could be poor indicators of ID in setting of inflammatory diseases or infection. They are also variable during daytime (i.e., serum iron).
- Serum soluble transferrin receptor (sTfR): sTfR derives from proteolysis of the membrane transferrin receptor. In case of ID, synthesis of transferrin receptors is increased, leading to a corresponding increase in sTfR (Table 4). A substantial advantage of measurement of sTfR compared with other assays is that it appears to be less influenced by ongoing inflammation [5]. However, this test is not available in all clinical laboratories; it is rather expensive and non-standardization of the measure constitutes a major disadvantage. Despite these restrictions, normal values have been published for healthy children and adolescents [92, 93].

Table 4 Parameters for iron deficiency analysis, blood volumes required and costs (OFAS taxpoint values). *Conversion CHF to EUR of 25.11.2019 and normal values of serum ferritin by turbidimetric assay (modified from Bohn et al. 2019 [90]); **could possibly reflect a sub-cohort of iron-deficient females

	Iron deficiency	Blood volume	Cost (CHF/EUR*)
Serum ferritin (see values below)	↓	0.1 mL	8/7
Age	Female (picoml/L)	Male (picoml/L)	
0 to < 1 month	337	337	
1 to < 6 months	19	19	
6 months to < 15 years	31	31	
15 to < 19 years	9**	47	
Soluble transferrin receptor	↑	1–3 mL	87/80
Zinc protoporphyrin	↑ or normal	4–5 mL	53/48
Serum iron	Fluctuations during the day	1 mL	3/2
Blood count	Interpretation complex MCV ↓ Hb (normal to) ↓ RDW ↑ MCH ↓	0.2 mL	9/8
Reticulocytes	↓	0.2 mL	13/12

- Zinc protoporphyrin (ZnPP): In cases of iron depletion, zinc transport across the intestinal barrier increases. Thus, an increased concentration of ZnPP in erythrocytes is associated with iron deficiency anemia [5]. Its increase (> 70 μmol/mol heme in children < 5 years old and > 80 μmol/mol heme in > 5 years old) therefore indicates ID-erythropoiesis [70]. ZnPP is also increased in lead poisoning or sideroblastic anemia. Unfortunately, this test is not available in all clinical laboratories and is rather expensive.
- Reticulocyte hemoglobin content (CHr or RET-He). CHr is an early marker of erythropoietic activity because reticulocytes are the first cells released into the circulation [94]. CHr is considered a real-time marker of functional ID, as reticulocytes only remain in blood for 1 to 2 days. This is a very sensitive and cost-effective test, available on most of the new generation hematology analyzers [93, 95]. This parameter has different names according to the brand name of the analyzer (i.e., "RET-He" for Sysmex machines, or "CHr" for ADVIA machines). In children, a CHr cutoff of 27.5 pg has high specificity and sensitivity for the diagnosis of ID in infants and toddlers (< 28 pg in older children and adults) [70, 92]

In cases of refractory ID/IDA after a trial of well conducted oral substitution (cf. below sections on ID therapy), it could be indicated to further investigate the following:

- C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR), in order to exclude infection or concomitant inflammatory disease, if not previously performed,
- Uristix and hemoccult in order to exclude urinary blood loss gastrointestinal disease respectively.
- A clinical bleeding score and a gynecological consultation should be performed in case of heavy menses (menometrorrhagia) in female adolescents is always indicated.

If there is still persistence of ID/IDA despite a well-tolerated oral substitution in a compliant patient/family, a consultation with a pediatric hematologist is strongly advised. The aim will be to rule out hemoglobinopathies or other primary erythroid/erythropoietic disorders, myelodysplastic syndrome, and B12 or folate deficiency. Abnormal iron absorption caused by gastrointestinal disease has been increasingly recognized as an important cause of unexplained ID. The recent availability of convenient, non-invasive screening methods to identify celiac disease, autoimmune atrophic gastritis, and *Helicobacter pylori* infection has greatly facilitated the recognition of patients with these entities [96]. Iron absorption is often limited in short bowel syndrome after surgical resection and can be a first symptom of IBD. In addition, in girls with IDA, an underlying menorrhagia (i.e., combined with a coagulopathy such as von Willebrand disease) can also be present [97].

Treatment of ID (IDWA and IDA)

Nutritional recommendations

In an asymptomatic child with ID alone, we recommend improving the dietary iron intake, by educating the family and providing nutritional recommendations. The best source of iron in food is "heme iron" found at high concentrations in animal sources with a bioavailability of about 20% (Table 5). Non-heme iron is available from most food sources, albeit with a lower bioavailability of about 5%. However, there are

good alternatives to heme iron with relatively high content of iron, e.g., legumes such as lentils, chickpeas or white or soya beans, wheat bran, or nuts. Iron absorption can be improved by adding different forms of acid to food, e.g., ascorbic acid in orange, lemon or grapefruit juice, or non-ascorbic acid sources such as apples, grapes or gooseberries, lemons, pears, or raspberries. Tannins in coffee, tea or wine, oxalate in spinach, rhubarb or cacao, and phosphate in soda drinks have been described as inhibitors of non-heme iron absorption. Most importantly, proteins in milk or egg white also inhibit intestinal iron absorption. In addition, macroglobulins in cows' milk can cause intestinal microhemorrhage in newborns and toddlers and bind and absorb iron-molecules in the gut [98, 99].

Oral iron therapy

Oral iron substitution is effective in the large majority of children with IDA and should always be initiated when a clear-cut laboratory diagnosis is established. Side effects can occur but are never dangerous. Detailed education and information of the family regarding possible side effects (constipation, some upper GI-irritation initially, tainting of teeth) at the beginning of therapy is strongly recommended, as it will help to improve adherence.

Before starting oral iron therapy, correction of any underlying nutritional problem has priority. In toddlers, we recommend reducing the intake of cows' milk. In children who are breastfed and/or receive formula, introduction of solid nutrition is advised at the age of 6 months (iron and vitamin content of breast milk >4 months is by then decreasing). In adolescents, we recommend reducing the intake of tea, soft drinks/sodas or supplements of phytates, oxalates, etc. Pediatricians need to be aware of vegetarian/vegan diets and provide nutritional education when appropriate. We recommend increasing daily fluid intake. It is important to note that Fe^{2+} and Fe^{3+} are both active iron compounds; however, they need to be dosed differently [100–102]:

- Oral Fe^{2+} supplementation: Give 2–3 mg/kg of elemental Fe^{2+} iron, in one or two doses/day, half an hour before or half an hour after the meal. Juice or water can be used to improve taste.
- Oral Fe^{3+} supplementation: Give 3–5 mg/kg of elemental Fe^{3+} iron, in one or two doses/day with meals (best is to drink juice or water with it; polymaltose is a sugar complex and needs to be dissolved in the gastric fluid to make the iron available in the intestines).

For children, there are liquid iron and capsules/tablets available. In older kids, consider also Fe^{2+} capsules/tablets that get resorbed in the intestines. Iron preparations available in Switzerland for children are listed in Table 6.

The recommended duration of oral iron substitution is 2–3 months. Monitoring therapy response is only necessary in cases with severe anemia or continuous iron losses (i.e., menorrhagia) or in case of suspected poor/insufficient adherence. In patients with IDA, therapy duration should be adapted to achieve normalization of Hb levels, MCV, and reticulocyte counts but also replete iron stores (i.e., normalized SF levels after correction of any anemia).

Actions in case of side effects or non-adherence

In our experience, switching from a Fe^{2+} to Fe^{3+} preparation can occasionally be helpful. Pediatricians need to be aware of the different dose recommendations (see above). If using Fe^{3+} preparations, consider changing from drops to suspension or vice versa, as tolerance/adherence patterns might vary in individual patients. Recent data from adult settings suggest that switching to an alternate-day schedule (taking the iron supplement every other day) might reduce GI side effects while still providing an equivalently effective iron substitution [103–105]. In fact, in a recent trial in adult anemic women with ID, alternate day dosing of oral iron supplements was shown to be more effective, as it increased fractional iron absorption by avoiding the preserved physiological peak of hepcidin, without any significant differences in the incidence of gastrointestinal side effects [105]. While there no evidence on alternate-day schedule dosing of oral iron in pediatrics, such strategy could be explored clinically on an individual

Table 5 Animal and vegetal iron sources and iron content (modified from reference [3])

Source	Iron content (in mg Fe) per 100 g
Animal sources: bioavailability about 20%	
Liver (pork or veal)	18
Dry beef	9.8
Shells	8.0
Egg yolk	5.5
Beef filet	2.3
Trout	2.0
Chicken	0.7
Vegetarian sources: bioavailability about 5%	
Wheat bran	16.0
Seeds of sesame	14.6
Soya beans	9.7
Lentils	8.0
White beans	7.0
Dried apricots	5.2
Spinach*	2.7
Whole grain bread	2.4
Green beans	1.0

*Limited value due to oxalate content

basis. A switch to IV iron should be restricted to cases with severe anemia (Hb < 70 g/L) in order to avoid transfusion, in cases with an underlying secondary disease fulfilling a formal indication for IV iron (IBD, chronic GI/GU bleeding, celiac disease, etc.) and/or in situations of non-adherence and symptomatic refractory IDA with clinical impact. The detailed indications for IV iron substitution in children are discussed below.

Intravenous iron therapy

Intravenous (IV) iron infusion is the only alternative to oral administration, as intramuscular iron injections have long been abandoned due to their association with pain, abnormal skin coloration, and the potential risk of sarcoma development at the injection sites (observed in animal models). Main benefits of IV iron therapy are (a) the avoidance of adherence challenges related to taste and GI side effects and (b) the bypassing of the intestinal mucosal barrier. In addition, the hemoglobin response is better after IV iron infusion when compared to oral iron, as documented in several studies [106].

Over the last two decades, there has been a significant evolution in the quality of parenteral iron products. First-generation IV iron preparations presented with unfavorable safety profiles. Associated with severe acute reactions, they were considered unsuitable for use in pediatrics. With iron dextran for example, severe acute reactions (i.e., anaphylaxis, respiratory arrest, and hypotension) occurred at a rate of approximately 1%, and thus, iron dextran was removed from the markets in 1991. The boom in the development of IV iron products resulted from the needs in the field of nephrology, and the patients affected by renal failure requiring dialysis. In this setting, the advent of recombinant human erythropoietin created a requirement for improved parenteral formulation to provide iron supplementation. In the mid to late 1990s, not only two low/high-molecular weight iron dextrans, but also two iron salts (ferric gluconate and iron sucrose) were licensed. The latter rapidly became market leaders, although the low-molecular weight iron dextrans proved to be safe [107, 108]. The most recent development has been in "optimized" formulations, where a reduced number of infusions are needed to achieve the delivery of an optimal dose of iron (i.e., ferric carboxymaltose), and short infusion times have been proven to be safe. At this time point, two IV iron products are available in Switzerland:

- Iron sucrose, authorized from the age of 3 years
- Iron carboxymaltose (ferric carboxymaltose, FCM), authorized from the age of 18 years (and from 14 years in Europe).

In adults, IV iron has been shown to (a) be a safe and effective adjunct to erythropoietin stimulating agents in chemotherapy induced anemia or dialysis for chronic kidney disease, (b) improve anemia in patients who underwent bariatric surgery, (c) be more effective and less toxic than oral iron in patients with ID associated to obstetrical and gynecological disorders, (d) correct anemia in patients with chronic bleeding where the iron loss is greater than oral iron can supply, or (e) be effective in those who are intolerant of oral iron formulations. Data on these areas of IV iron use is available in many reviews out of the scope of this paper and still in constant evolution. In fact, a recent systematic Cochrane review has for example challenged the role of IV iron in reducing postoperative transfusions when administered preoperatively to anemic patients undergoing elective surgery [109].

Safety of IV iron in children

Although most safety data for IV iron at this time results from studies in adults, the reported incidence of side effects (mainly anaphylactic reactions) with newer generation IV iron products is lower than for previous generation agents (such as high molecular weight dextrans). Data from studies in adults show that IV iron is contraindicated in the course of infections, in the first trimester of pregnancy, and in patients with a history of iron or of another significant (i.e., anaphylactic) drug allergy. Immediate side effects of an IV iron infusion can be nausea, vomiting, headache, flushing, myalgia, pruritus, arthralgia, and back and chest pain. Hypophosphatemia can be observed but is usually transient and asymptomatic, and there are no guidelines on its prevention. Sometimes, skin complications have occurred at the site of injection in children even with the recent generation formulations [110]. The only data available on long-term toxicities of IV iron use are from adult hemodialysis patients, where numerous analyses have identified no long-term morbidity or increased incidence of infections [111–113]. In adults, the observed persistence of very high SF levels (> 500 mcg/L) for 1–2 weeks after IV iron (carboxymaltose) seems to be without consequences [114].

There has been a very significant increase in the evidence supporting the safety of parenteral iron products in children over the last decade [115, 116]. A retrospective analysis of IV iron administered to patients for iron replacement therapy at a tertiary pediatric hospital (nephrology patients excluded) showed that in a total of more than 1000 doses administered to almost 200 patients over 6 years, a majority of patients (approx. 70%) required multiple infusions and dosing was highly variable, ranging from 1.3 to 1030 mg per infusion [117]. Specialties mostly involved were gastroenterology and hematology, with IBD as the most frequent indication. Premedication use was infrequent (approx. 10% of doses), and no severe infusion-associated reactions occurred. These data show that IV iron is commonly prescribed by certain pediatric specialties, but there is little standardization in the indications, formulations, or dosing. These data suggest that

Table 6 Oral iron formulations available in Switzerland (liquid preparations and tablets/capsules with Fe content < 70 mg/tablets) for children, according to Swiss Drug Compendium and List of Specialties [LS], July 2019. All of the products listed herein are given for information only and do not represent an endorsement or specific recommendation by the authors. *Child of 30 kg with a Hb = 70 g/L, 6 months therapy with Fe^{2+} at 3 mg/kg/day and Fe^{3+} at 5 mg/kg/day

Product	Company	Compound	Galenics	Dose (Fe)	Price (LS)	Price for typical therapy course*
Aktiferrin	Mepha	Fe^{2+} sulfate	Suscaps	34 mg	Not reimbursed in CH	N/A
			Drops	1 mL = 10 mg = 13 drops	Not reimbursed in CH	N/A
Tardyferon	Pierre Fabre	Fe^{2+} sulfate	Slow release tablets	80 mg	8.60 CHF/original package 0.29 CHF/tablet	CHF 59
Maltofer	Vifor	Fe^{3+} polymaltose	Syrup	1 mL = 100 mg	11.05 CHF/original package 0.07 CHF/mL	CHF 19
			Drops	1 mL = 50 mg = 20 drops	9.20 CHF/original package 0.30 CHF/mL	CHF 162
			Coated tablets	100 mg	12.65 CHF/original package 0.42 CHF/tablet	CHF 113
			Chewable tablets	100 mg	12.65 CHF/original package 0.42 CHF/tablet	CHF 113
Duofer	Andreabal	Fe^{2+} acidum ascorbicum	Coated tablets	69 mg	12.60 CHF/original package 0.32 CHF/tablet	CHF 75
Duofer Fol	Andreabal	Fe^{2+} acidum ascorbicum + acidum folicum	Coated tablets	69 mg	16.20 CHF/original package 0.40 CHF/tablet	CHF 94
Ferrum Hausmann	Vifor	Fe^{2+} fumarate	Capsules	100 mg	8.80 CHF/original package 0.30 CHF/capsule	CHF 49

IV iron could be considered a safe alternative for iron deficiency treatment in pediatrics when oral iron is either unsuccessful or (as in rare occasions) contraindicated. No long-term follow-up evidence of increased SF levels in children post-IV iron infusion is available, and therefore, their potential impact is unknown. Interestingly, in the recent German KIGGS study where laboratory results were correlated with information from interviews with children and parents, it also found inferior psychosocial parameters (i.e., quality of life assessment scores, peer interaction and school performance) in children with high (> 97th percentile) ferritin and low (< 10th percentile) sTFR levels [118, 119]. This could suggest a potential adverse effect of long-standing hyperferritinemia and a need for a more stringent indication for recurrent intravenous iron administration or at least attentive post-marketing follow-up. However, no long-term prospective studies have been published so far on this matter.

Safety precautions for the IV administration of iron to children

Some precautions are required for the safe administration of IV iron products. Recommendations on how to minimize the risk of IV iron infusions in adults have been published [120]. They include careful patient monitoring (pre- to post-administration) in an adequate clinical environment with trained staff, slower infusion rates, and requirement of standing premedication. Our group recommends that, in children, an IV iron infusion should be performed on the order of a specialist with expertise and experience (in pediatric iron metabolism incl. pediatric life-support, PALS), having established an indication after a clinical and paraclinical assessment, under monitoring of vital parameters, in a structure equipped with adequate pediatric-specific resuscitation devices and infrastructure [121]. Our group recommends that anti-anaphylaxis medications (i.e., antihistamines, steroids and epinephrine) should be available and ready to use without delay when IV products are infused in children. Our group strongly opposes the concept of "iron infusion clinics" for children and adolescents, as they constitute potential hurdles in the timely and accurate diagnosis of harmful underlying conditions in this vulnerable age group. Our recommendation is that patients receiving IV iron in the pediatric age should always benefit from consultation of pediatric hematologist (or specialist of iron metabolism) and specialist of any underlying condition.

Pediatric areas with clear indications for intravenous iron use

First, in patients with IBD in whom oral iron worsens bowel symptoms, IV iron has been shown to be an effective, safe, and a less toxic alternative [122–126]. This is also the case for more recent formulations as ferric carboxymaltose. In a recent study, 101 children affected by IBD with IDWA or IDA were treated prospectively [127]. Following the iron infusion, 64% of patients with IDA had resolution of anemia, with 81% showing resolution for ID without anemia. Importantly, in this inflammatory context, elevation of C-reactive protein was shown not to influence the resolution of IDA, but this was not the case in ID alone. This data has been confirmed in its safety aspects by others [128].

Second, children undergoing dialysis for chronic kidney disorders benefit from IV iron, and there is evidence to show that it is safe and effective to administer it in such a setting [129–134]. This might be the case also for children with chronic kidney disease not yet receiving erythropoietin stimulating agents [135]. In children after renal transplantation, IV iron has been shown to be effective and safe [136, 137]. This could be of value for other solid transplant recipients [138]. The rapid infusion of IV sucrose has been proven safe in children with chronic kidney impairment [139].

Third, recently IV iron has even been shown to correct the symptoms of patients with RLS in both ID and iron replete individuals [48, 140, 141]. The International Restless Leg Syndrome Study Group (IRLSSG) task force, based on clinical experience and solid data in adult RLS, recommends that IV iron sucrose (3–6 mg/kg; max 120 mg) can be considered for pediatric RLS/Periodic Limb Movement Disorder (PLMD) if performed in the setting of an infusion center with pediatric experience and provided the following occur: a prior oral iron treatment of at least 3 months has not produced an adequate benefit or was discontinued because of adverse effects and there has been no appreciable rise in serum ferritin levels with 3 months of oral iron treatment. IV iron can be considered without a prior oral iron trial if significant comorbidity is present that will impair iron absorption. A serum ferritin ≥ 50 mcg/L is considered an adequate therapeutic target in children.

Areas in which IV iron use is debated

The role of IV iron administration in children with IDA as a first-line therapy has been debated for many years [142, 143]. A retrospective review of 37 children with IDA refractory to oral iron effectively showed the ease of administration and effectiveness of IV iron sucrose to correct the anemia [144]. Interestingly, the majority of these children had gastrointestinal toxicity from oral iron preparations. In a retrospective cohort study, a total of 116 IV iron carboxymaltose infusions were administered to 72 patients with IDA refractory to oral iron and were shown to be safe and highly effective in a small yet diverse population of infants, children, and adolescents [145, 146]. Smaller monocentric retrospective studies also suggest similar safety profiles and suggest that patients with malabsorption (not otherwise specified) can benefit from such

an approach [147, 148]. Interestingly, benefit was also noted when the IV product used was not one of the most recent generation [149, 150]. In a Turkish single center prospective study, a small ($n = 62$) cohort of children with pre-operative IDA, where oral iron administration was considered not feasible for reasons ranging from poor adherence to socio-cultural factors, was given IV iron sucrose [151]. Results showed a rapid increase in hemoglobin and a notable rate of 12% of adverse events, the majority of whom were minor (rashes, fever, irritability). Nonetheless, the question of pre-operative IV iron versus oral iron or red cell transfusion has not been addressed in a prospective, randomized fashion and little published evidence exists to guide decision-making for children.

In physically very active children (i.e., young athletes), the use of IV iron has been the focus of much debate. A recent consensus paper of the Swiss Society of Sports Medicine has reviewed iron metabolism in athletes in detail, and has defined specific cutoff values suggesting ID/IDA, but has refrained from recommending anything else than oral iron supplementation [152]. It is worth of note that IV iron infusions in athletes have to respect the anti-doping regulations of the World Anti-Doping Agency if these individuals desire to participate in competitive events.

In neonates and young toddlers, there is discussion about possible oxidative stress induction to blood components and endothelial structures. Several authors do recommend to avoid intravenous iron in neonates and infants [153].

IV iron use in IRIDA versus URIDA

In a Turkish single center prospective study, a small ($n = 11$) cohort of children with oral IRIDA (with TMPRSS6 mutations) was analyzed to measure the response to IV iron sucrose therapy [154]. Both Hb and SF levels increased after therapy, but surprisingly, SF continued to increase at 6 months after the first and 6 weeks after the second infusion, respectively, suggesting that in such setting, continued administration of IV iron would be of no benefit to increase Hb levels but could further lead to long-lasting hyperferritinemia. A follow-up study compared these findings with the same intervention performed in a cohort of 15 children with unexplained refractory iron deficiency anemia (URIDA) [155]. The results suggest that the response to IV iron therapy in URIDA was more significant that in hereditary IRIDA and that measuring the response to parenteral iron therapy would be helpful to distinguish these conditions when hepcidin assays or TMPRSS6 mutation analysis are not routinely available. Until the biology behind those therapy responses are better understood, we do not recommend using IV iron infusion as a mean to diagnose, confirm, or distinguish IRIDA/URIDA.

Post-infusion efficacy verification

The efficacy of the parenteral iron treatment can be measured by the reticulocyte response (increased reticulocyte levels) after 5–10 days from the infusion. An increase in the CHr has also been observed by various authors: for some, an increase in CHr is described as early as 48 h but in any case, within 2 weeks of the infusion. An iron status assessment should nevertheless be repeated after 8–12 weeks in parenteral iron therapy to verify SF levels and exclude persistent hyperferritinemia.

Cost-effectiveness

Cost-effectiveness and reimbursement issues should be discussed openly with the families. Of note, certain healthcare insurances refuse coverage for IV iron formulations in children, especially when their use is "off label." In fact, costs vary, and all IV formulations are substantially more expensive than oral iron therapy, excluding the costs related to the associated clinical surveillance (Table 7). A study in Switzerland has shown that the healthcare costs related to IV iron infusions have markedly increased (by 340%)during the 5-year observation period and the number of individuals treated as well (by 244%) [156]. It appears that more than 8% of IV iron infusions were administered without prior laboratory analysis and must therefore be regarded as off-label use. This explosion in use and cost occurred without a cost-benefit analysis demonstrating the additional value of IV over oral iron supplementation in these patient populations.

Summary of recommendations for IV iron supplementation in children

IV iron administration can be considered as *first-line strategy* in the following specific situations:

- Chronic intestinal inflammatory disease or situations with proven malabsorption
- Chronic kidney disease on hemodialysis under ESA or without ESA
- Chronic bleeding/spoliation with an uncorrectable etiology, where oral therapy is insufficiently effective or contraindicated

Treatment with IV iron in children is currently possible according to international guidelines as a *second-line strategy* after consultation with a specialist in pediatric iron metabolism (certified pediatric hematologist) under specific conditions:

- Failure to achieve correction of IDA after well-conducted oral iron substitution, in the setting of good adherence (at

least 6 months of prescrived supplementation, and two formulation attempts)
- Confirmed malabsorption or chronic oral iron intolerance, including the category of children with severe neurological/neurodevelopmental impairments leading to feeding limitations

Contraindications for IV iron in children

Contraindications for IV iron use are:

- Presence of an active/acute infection
- Personal history of drug anaphylaxis/allergy
- Tractable comorbidity explaining the signs and symptoms (i.e., neurological, psychiatric and psychosomatic/functional disorders)
- A desire to increase school/academic or sports performance (constituting de facto "doping") in the absence of laboratory tests confirming ID

Thresholds and dosing of IV iron in children

Thresholds for IV iron supplementation should be the identical to those for oral iron use once a clear indication (see above) is met, unless there is an underlying condition where the interpretation of iron stores is limited/impossible or the condition's clinical impact warrants differently. The amount of iron to be substituted is based on the patient's weight and should be calculated according to the Ganzoni formula (Table 8; also see Swiss Drug Compendium, a pediatric specific calculation system is available).

Recommendations regarding IV product choice in children

Choice of the IV product should be based on the indications listed in the approved drug list (LS: LSpec/SpezL for Switzerland http://www.spezialitaetenliste.ch, or the Swiss Drug Compendium, www.compendium.ch). As such, the only product registered for children in Switzerland is iron sucrose. Off-label use can exceptionally be considered for other registered products on the LS, but warrants careful discussion, expert involvement, and consideration of risk/benefit.

Regarding the off-label use of IV iron, it needs to be stated clearly that the prescribing physician assumes all responsibility of any resulting serious adverse event, and informed consent is imperative as for all procedures and medications.

Table 8 Calculation of IV iron in children (Ganzoni formula)

Total iron deficiency [mg] = Cumulative total dose =
Body weight[kg] × (Target Hb − Measured Hb)[g/dL] × 2.4
+ iron reserves [mg]

Target Hb and iron reserves:
Body weight < 35 kg: Hb target 13 g/dL; iron stores 15 mg/kg
Body weight ≥ 35 kg: Target Hb 15 g/dL; iron stores 500 mg

Recommendations on the monitoring of post-IV iron therapy in children

The need for clinical and laboratory follow-up of post-IV iron therapy in children depends on the underlying indication(s) for replacement and/or supplementation, the chosen IV iron formulation, as well as the patient's clinical response to and tolerance of the drug. In pediatric clinical practice, the two following scenarios are most frequently encountered:

First, in children where a chronic co-morbidity (e.g., IBD) causes a prolonged requirement of IV iron supplementation, the administration and follow-up schedule will need to be determined by the clinical course of the underlying condition (e.g., presence/severity of IBD-related GI blood loss) and/or the patient's individualized need for IV iron therapy over time. Acute and chronic phases of the underlying condition modulate the need for surveillance and the schedule of IV iron infusions. Disease-specific recommendations for the monitoring of IV iron therapy should always be followed when available, and evidence is growing in many pediatric areas of care. Their review is beyond the scope of this paper. Nonetheless, we strongly recommend the involvement of a pediatric hematologist or iron metabolism specialist in such situations. She/he should actively discuss and collaborate with the subspecialist responsible for the care of the underlying disease in managing the patient and designing effective and safe IV iron infusion schedules. In situations with

Table 7 Brand name and costs for IV iron preparations available in Switzerland (according to Swiss Drug Compendium und List of Specialties (LS), conversion CHF to EUR of 25.11.2019); *as calculated by the Ganzoni Formula (Table 8), excluding the costs of provision of care. All of the products listed herein are given for information only and do not represent an endorsement or specific recommendation by the authors

Brand name	Dosage	Price (in CHF)	Price (in EUR)	Price per mg (in EUR)	Price for therapy of a 30 kg child with Hb of 8 g/dL (810 mg)*	Comments
Venofer	100 mg/5 mL	22.70	20.70	0.2	162	Registered for children ≥ 3 years
Ferinject	100 mg/2 mL	35.50	32.30	0.3	243	Off-label in children
Ferinject	500 mg/10 mL	164.30	149.5	0.3	243	Off-label in children

insufficient pediatric data, evidence can sometimes be extrapolated from the adult literature, and guidance safely used in children. To serve as an illustrative example, adult patients with IBD should be monitored for ID on a monthly basis while in active disease status as a minimum. In clinically controlled IBD, recurrence of ID should be excluded every 3 months for at least 1 year following correction of iron stores and at least every 6–12 months thereafter. Laboratory tests should include Hb, SF, transferrin saturation, and CRP. Drops of SF or Hb below normal ranges should trigger iron therapy. These recommendations are frequently used for the monitoring of IV iron therapy in children with IBD and have proven to be reliable in the prevention of ID in this condition.

Second, in children where IV iron therapy is used for indications that remain debated, follow-up will depend on the desired clinical result and the chosen product, but a clinical exam with laboratory testing including a complete blood count with reticulocytes and an iron panel 1-month post-infusion is recommended and constitutes the minimum. In this setting, patients and their families should always be encouraged to re-consider transitioning back to oral iron therapy as soon as possible. Any additional IV iron dose will have to be carefully discussed, as indicated above.

Conclusion

Iron deficiency with and without anemia is a common issue in childhood. In this review, we provide concrete management recommendations for the pediatrician based on the best evidence available, including diagnosis and therapy, both for oral and intravenous administrations. These considerations and recommendations result from the consensus of a group of Swiss pediatric hematologists. Of course, pediatric medicine is an ever-changing field, and 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.

Author contribution VM, MS, HH, NvdW, and RR reviewed and interpreted the evidence and drafted sections of the manuscript. RR wrote the final manuscript, after comprehensive editing. All authors discussed, reviewed, and agree with the final manuscript.

Funding information Vifor Pharma SA provided unrestricted support for the three working group meetings to draft this manuscript but had no input in the content of the manuscript and did not influence the discussions at the meetings.

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. WHO (2016) Guideline: daily iron supplementation in infants and children. In: Committee GR (ed) World Health Organization (WHO). Switzerland, Geneva
2. Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux S (2015) Nathan and Oski's hematology of infancy and childhood, 8th edn. Saunders, Philadelphia
3. Domellof M, Braegger C, Campoy C, Colomb V, Decsi T, Fewtrell M, Hojsak I, Mihatsch W, Molgaard C, Shamir R, Turck D, van Goudoever J, Nutrition ECo (2014) Iron requirements of infants and toddlers. J Pediatr Gastroenterol Nutr 58: 119–129
4. Sekhar DL, Murray-Kolb LE, Kunselman AR, Weisman CS, Paul IM (2017) Association between menarche and iron deficiency in non-anemic young women. PLoS One 12:e0177183
5. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L (2016) Iron deficiency anaemia. Lancet 387:907–916
6. Global Burden of Disease Pediatrics C, Kyu HH, Pinho C, Wagner JA, Brown JC, Bertozzi-Villa A, Charlson FJ et al (2016) Global and national burden of diseases and injuries among children and adolescents between 1990 and 2013: findings from the global burden of disease 2013 study. JAMA Pediatr 170:267–287
7. Auerbach M, Adamson JW (2016) How we diagnose and treat iron deficiency anemia. Am J Hematol 91:31–38
8. Camaschella C (2017) New insights into iron deficiency and iron deficiency anemia. Blood Rev 31:225–233
9. Beard J (2003) Iron deficiency alters brain development and functioning. J Nutr 133:1468S–1472S
10. Lukowski AF, Koss M, Burden MJ, Jonides J, Nelson CA, Kaciroti N, Jimenez E, Lozoff B (2010) Iron deficiency in infancy and neurocognitive functioning at 19 years: evidence of long-term deficits in executive function and recognition memory. Nutr Neurosci 13:54–70
11. Musallam KM, Taher AT (2018) Iron deficiency beyond erythropoiesis: should we be concerned? Curr Med Res Opin 34:81–93
12. Vallee L (2017) Iron and neurodevelopment. Arch Pediatr 24: 5S18–15S22
13. Sachdev H, Gera T, Nestel P (2005) Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials. Public Health Nutr 8: 117–132
14. Pratt JJ, Khan KS (2016) Non-anaemic iron deficiency - a disease looking for recognition of diagnosis: a systematic review. Eur J Haematol 96:618–628
15. Szajewska H, Ruszczynski M, Chmielewska A (2010) Effects of iron supplementation in nonanemic pregnant women, infants, and young children on the mental performance and psychomotor development of children: a systematic review of randomized controlled trials. Am J Clin Nutr 91:1684–1690
16. Angulo-Barroso RM, Li M, Santos DC, Bian Y, Sturza J, Jiang Y, Kaciroti N, Richards B, Lozoff B (2016) Iron supplementation in pregnancy or infancy and motor development: a randomized controlled trial. Pediatrics 137:e20153547
17. Friel JK, Aziz K, Andrews WL, Harding SV, Courage ML, Adams RJ (2003) A double-masked, randomized control trial of iron supplementation in early infancy in healthy term breast-fed infants. J Pediatr 143:582–586
18. Lind T, Lonnerdal B, Stenlund H, Gamayanti IL, Ismail D, Seswandhana R, Persson LA (2004) A community-based randomized controlled trial of iron and zinc supplementation in

Indonesian infants: effects on growth and development. Am J Clin Nutr 80:729–736
19. Moffatt ME, Longstaffe S, Besant J, Dureski C (1994) Prevention of iron deficiency and psychomotor decline in high-risk infants through use of iron-fortified infant formula: a randomized clinical trial. J Pediatr 125:527–534
20. Olney DK, Pollitt E, Kariger PK, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Stoltzfus RJ (2006) Combined iron and folic acid supplementation with or without zinc reduces time to walking unassisted among Zanzibari infants 5- to 11-mo old. J Nutr 136:2427–2434
21. Oski FA, Honig AS (1978) The effects of therapy on the developmental scores of iron-deficient infants. J Pediatr 92:21–25
22. Stoltzfus RJ, Kvalsvig JD, Chwaya HM, Montresor A, Albonico M, Tielsch JM, Savioli L, Pollitt E (2001) Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study. BMJ 323:1389–1393
23. Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L (2010) The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. Nutr J 9:4
24. Mattiello V, Sizonenko S, Baleydier F, Bernard F, Diezi M, Renella R (2019) Iron deficiency with and without anemia in children: a brief update for caregivers. Rev Med Suisse 15:376–381
25. Cook RL, O'Dwyer NJ, Parker HM, Donges CE, Cheng HL, Steinbeck KS, Cox EP, Franklin JL, Garg ML, Rooney KB, O'Connor HT (2017) Iron deficiency anemia, not iron deficiency, is associated with reduced attention in healthy young women. Nutrients 9:E1216
26. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG (2001) Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. Pediatrics 107:1381–1386
27. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J (1996) Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. Lancet 348:992–996
28. Felt BT, Biermann B, Christner JG, Kochhar P, Harrison RV (2014) Diagnosis and management of ADHD in children. Am Fam Physician 90:456–464
29. Konofal E, Lecendreux M, Deron J, Marchand M, Cortese S, Zaim M, Mouren MC, Arnulf I (2008) Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatr Neurol 38:20–26
30. Calarge C, Farmer C, DiSilvestro R, Arnold LE (2010) Serum ferritin and amphetamine response in youth with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 20:495–502
31. Cortese S, Konofal E, Bernardina BD, Mouren MC, Lecendreux M (2009) Sleep disturbances and serum ferritin levels in children with attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry 18:393–399
32. Demirci K, Yildirim Bas F, Arslan B, Salman Z, Akpinar A, Demirdas A (2017) The investigation of symptoms and diagnoses of adult-attention deficit/hyperactivity disorder in women with iron deficiency anemia. Noro Psikiyatr Ars 54:72–77
33. Islam K, Seth S, Saha S, Roy A, Das R, Datta AK (2018) A study on association of iron deficiency with attention deficit hyperactivity disorder in a tertiary care center. Indian J Psychiatry 60:131–134
34. Juneja M, Jain R, Singh V, Mallika V (2010) Iron deficiency in Indian children with attention deficit hyperactivity disorder. Indian Pediatr 47:955–958
35. Konofal E, Lecendreux M, Arnulf I, Mouren MC (2004) Iron deficiency in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 158:1113–1115
36. Turner CA, Xie D, Zimmerman BM, Calarge CA (2012) Iron status in toddlerhood predicts sensitivity to psychostimulants in children. J Atten Disord 16:295–303
37. Romanos M, Tiesler CM, Koletzko S, Berdel D, von Berg A, Hoffmann B, Schaaf B, Herbarth O, Lehmann I, Bauer CP, Stach B, Gerlach M, Schulte-Korne G, Heinrich J (2013) No cross-sectional and longitudinal association of ferritin and symptoms of attention-deficit-/hyperactivity disorder in a large population-based sample of children: results from the GINIplus and LISAplus studies. Atten Defic Hyperact Disord 5:313–320
38. Wang Y, Huang L, Zhang L, Qu Y, Mu D (2017) Iron status in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. PLoS One 12:e0169145
39. Sever Y, Ashkenazi A, Tyano S, Weizman A (1997) Iron treatment in children with attention deficit hyperactivity disorder. A preliminary report. Neuropsychobiology 35:178–180
40. Tseng PT, Cheng YS, Yen CF, Chen YW, Stubbs B, Whiteley P, Carvalho AF, Li DJ, Chen TY, Yang WC, Tang CH, Chu CS, Yang WC, Liang HY, Wu CK, Lin PY (2018) Peripheral iron levels in children with attention-deficit hyperactivity disorder: a systematic review and meta-analysis. Sci Rep 8:788
41. El-Baz FM, Youssef AM, Khairy E, Ramadan D, Youssef WY (2019) Association between circulating zinc/ferritin levels and parent Conner's scores in children with attention deficit hyperactivity disorder. Eur Psychiatry 62:68–73
42. Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L (2007) Restless legs syndrome: prevalence and impact in children and adolescents–the Peds REST study. Pediatrics 120:253–266
43. Yilmaz K, Kilincaslan A, Aydin N, Kor D (2011) Prevalence and correlates of restless legs syndrome in adolescents. Dev Med Child Neurol 53:40–47
44. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB, International Restless Legs Syndrome Study G (2014) Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med 15:860–873
45. Earley CJ, Connor J, Garcia-Borreguero D, Jenner P, Winkelman J, Zee PC, Allen R (2014) Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis-Ekbom disease). Sleep Med 15:1288–1301
46. Stefansson H, Rye DB, Hicks A, Petursson H, Ingason A, Thorgeirsson TE, Palsson S, Sigmundsson T, Sigurdsson AP, Eiriksdottir I, Soebech E, Bliwise D, Beck JM, Rosen A, Waddy S, Trotti LM, Iranzo A, Thambisetty M, Hardarson GA, Kristjansson K, Gudmundsson LJ, Thorsteinsdottir U, Kong A, Gulcher JR, Gudbjartsson D, Stefansson K (2007) A genetic risk factor for periodic limb movements in sleep. N Engl J Med 357:639–647
47. Catoire H, Dion PA, Xiong L, Amari M, Gaudet R, Girard SL, Noreau A, Gaspar C, Turecki G, Montplaisir JY, Parker JA, Rouleau GA (2011) Restless legs syndrome-associated MEIS1 risk variant influences iron homeostasis. Ann Neurol 70:170–175
48. Allen RP, Picchietti DL, Auerbach M, Cho YW, Connor JR, Earley CJ, Garcia-Borreguero D, Kotagal S, Manconi M, Ondo W, Ulfberg J, Winkelman JW, International Restless Legs Syndrome Study G (2018) Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Med 41:27–44

49. Leung AKC, Leung AAM, Wong AHC, Hon KL (2019) Breath-holding spells in pediatrics: a narrative review of the current evidence. Curr Pediatr Rev 15:22–29
50. Jain R, Omanakuttan D, Singh A, Jajoo M (2017) Effect of iron supplementation in children with breath holding spells. J Paediatr Child Health 53:749–753
51. Kolkiran A, Tutar E, Atalay S, Deda G, Cin S (2005) Autonomic nervous system functions in children with breath-holding spells and effects of iron deficiency. Acta Paediatr 94:1227–1231
52. Zehetner A (2011) Iron supplementation reduces the frequency and severity of breath-holding attacks in non-anaemic children. Clin Pract 1:e98
53. Khan Y, Tisman G (2010) Pica in iron deficiency: a case series. J Med Case Rep 4:86
54. Borgna-Pignatti C, Zanella S (2016) Pica as a manifestation of iron deficiency. Expert Rev Hematol 9:1075–1080
55. Yadav D, Chandra J (2011) Iron deficiency: beyond anemia. Indian J Pediatr 78:65–72
56. Brown WD, Dyment PG (1972) Pagophagia and iron deficiency anemia in adolescent girls. Pediatrics 49:766–767
57. Hinton PS, Sinclair LM (2007) Iron supplementation maintains ventilatory threshold and improves energetic efficiency in iron-deficient nonanemic athletes. Eur J Clin Nutr 61:30–39
58. Hinton PS (2014) Iron and the endurance athlete. Appl Physiol Nutr Metab 39:1012–1018
59. Peeling P, Dawson B, Goodman C, Landers G, Wiegerinck ET, Swinkels DW, Trinder D (2009) Training surface and intensity: inflammation, hemolysis, and hepcidin expression. Med Sci Sports Exerc 41:1138–1145
60. Roecker L, Meier-Buttermilch R, Brechtel L, Nemeth E, Ganz T (2005) Iron-regulatory protein hepcidin is increased in female athletes after a marathon. Eur J Appl Physiol 95:569–571
61. Sinclair LM, Hinton PS (2005) Prevalence of iron deficiency with and without anemia in recreationally active men and women. J Am Diet Assoc 105:975–978
62. DellaValle DM, Haas JD (2011) Impact of iron depletion without anemia on performance in trained endurance athletes at the beginning of a training season: a study of female collegiate rowers. Int J Sport Nutr Exerc Metab 21:501–506
63. Sharma R, Stanek JR, Koch TL, Grooms L, O'Brien SH (2016) Intravenous iron therapy in non-anemic iron-deficient menstruating adolescent females with fatigue. Am J Hematol 91:973–977
64. Rowland TW, Deisroth MB, Green GM, Kelleher JF (1988) The effect of iron therapy on the exercise capacity of nonanemic iron-deficient adolescent runners. Am J Dis Child 142:165–169
65. Brutsaert TD, Hernandez-Cordero S, Rivera J, Viola T, Hughes G, Haas JD (2003) Iron supplementation improves progressive fatigue resistance during dynamic knee extensor exercise in iron-depleted, nonanemic women. Am J Clin Nutr 77:441–448
66. Brownlie T, Utermohlen V, Hinton PS, Haas JD (2004) Tissue iron deficiency without anemia impairs adaptation in endurance capacity after aerobic training in previously untrained women. Am J Clin Nutr 79:437–443
67. Gera T, Sachdev HP (2002) Effect of iron supplementation on incidence of infectious illness in children: systematic review. BMJ 325:1142
68. Murray MJ, Murray AB, Murray MB, Murray CJ (1978) The adverse effect of iron repletion on the course of certain infections. Br Med J 2:1113–1115
69. Tansarli GS, Karageorgopoulos DE, Kapaskelis A, Gkegkes I, Falagas ME (2013) Iron deficiency and susceptibility to infections: evaluation of the clinical evidence. Eur J Clin Microbiol Infect Dis 32:1253–1258
70. Zimmermann MB, Hurrell RF (2007) Nutritional iron deficiency. Lancet 370:511–520
71. Long H, Yi JM, Hu PL, Li ZB, Qiu WY, Wang F, Zhu S (2012) Benefits of iron supplementation for low birth weight infants: a systematic review. BMC Pediatr 12:99
72. Huang SC, Yang YJ, Cheng CN, Chen JS, Lin CH (2010) The etiology and treatment outcome of iron deficiency and iron deficiency anemia in children. J Pediatr Hematol Oncol 32:282–285
73. Camaschella C (2015) Iron-deficiency anemia. N Engl J Med 372: 1832–1843
74. Camaschella C (2019) Iron deficiency. Blood 133:30–39
75. Hershko C, Camaschella C (2014) How I treat unexplained refractory iron deficiency anemia. Blood 123:326–333
76. Polin V, Coriat R, Perkins G, Dhooge M, Abitbol V, Leblanc S, Prat F, Chaussade S (2013) Iron deficiency: from diagnosis to treatment. Dig Liver Dis 45:803–809
77. Hudson BH, Hale AT, Irving RP, Li S, York JD (2018) Modulation of intestinal sulfur assimilation metabolism regulates iron homeostasis. Proc Natl Acad Sci U S A 115:3000–3005
78. Ginzburg YZ (2019) New diagnostic tools for delineating iron status. Hematol Am Soc Hematol Educ Program 2019:327–336
79. Baker RD, Greer FR, Committee on Nutrition American Academy of P (2010) Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics 126:1040–1050
80. Committee UNS (2012) Screening for iron deficiency anaemia in children under 5 years of age. Version 2
81. Siu AL, Force USPST (2015) Screening for iron deficiency anemia in young children: USPSTF recommendation statement. Pediatrics 136:746–752
82. de Montalembert M, Bresson JL, Brouzes C, Ruemmele FM, Puy H, Beaumont C (2012) Diagnosis of hypochromic microcytic anemia in children. Arch Pediatr 19:295–304
83. Peyrin-Biroulet L, Williet N, Cacoub P (2015) Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. Am J Clin Nutr 102:1585–1594
84. Rubeor A, Goojha C, Manning J, White J (2018) Does iron supplementation improve performance in iron-deficient nonanemic athletes? Sports Health 10:400–405
85. (2016) Guideline: daily iron supplementation in infants and children, Geneva
86. Jonker FA, Boele van Hensbroek M, Leenstra T, Vet RJ, Brabin BJ, Maseko N, Gushu MB, Emana M, Kraaijenhagen R, Tjalsma H, Swinkels DW, Calis JC (2014) Conventional and novel peripheral blood iron markers compared against bone marrow in Malawian children. J Clin Pathol 67:717–723
87. Abdullah K, Birken CS, Maguire JL, Fehlings D, Hanley AJ, Thorpe KE, Parkin PC (2017) Re-evaluation of serum ferritin cut-off values for the diagnosis of iron deficiency in children aged 12-36 months. J Pediatr 188:287–290
88. Larsson SM, Hillarp A, Hellstrom-Westas L, Domellof M, Lundahl T, Andersson O (2019) When age really matters; ferritin reference intervals during infancy revisited. Scand J Clin Lab Invest 79:590–594
89. Daru J, Colman K, Stanworth SJ, De La Salle B, Wood EM, Pasricha SR (2017) Serum ferritin as an indicator of iron status: what do we need to know? Am J Clin Nutr 106:1634S–1639S
90. Quadri A, Gojanovic B, Noack P, Brunner S, Huber A, Kriemler S (2018) Esenmangel bei Sportlern – Neue Empfehlungen zur Abklärung und Therapie. Swiss Sports Exerc Med 66:26–29
91. Bohn MK, Higgins V, Asgari S, Leung F, Hoffman B, Macri J, Adeli K (2019) Paediatric reference intervals for 17 Roche cobas 8000 e602 immunoassays in the CALIPER cohort of healthy children and adolescents. Clin Chem Lab Med 57:1968–1979
92. Stuart H, Orkin DGN, David Ginsburg A, Look T, Fisher DE, Lux S (2015) Nathan and Oski's hematology of infancy and childhood, 8th edn. Saunders, Philadelphia

93. Vazquez-Lopez MA, Lopez-Ruzafa E, Ibanez-Alcalde M, Martin-Gonzalez M, Bonillo-Perales A, Lendinez-Molinos F (2019) The usefulness of reticulocyte haemoglobin content, serum transferrin receptor and the sTfR-ferritin index to identify iron deficiency in healthy children aged 1-16 years. Eur J Pediatr 178:41–49
94. Waldvogel Abramowski S, Favrat B, Vaucher P, Cornuz J, Tissot JD (2013) Diagnostic markers of iron deficiency: which should we choose? Rev Med Suisse 9:380–383
95. Thuret I (2017) Biological diagnosis of iron deficiency in children. Arch Pediatr 24:5S6–5S13
96. Hershko C, Skikne B (2009) Pathogenesis and management of iron deficiency anemia: emerging role of celiac disease, Helicobacter pylori, and autoimmune gastritis. Semin Hematol 46:339–350
97. Cooke AG, McCavit TL, Buchanan GR, Powers JM (2017) Iron deficiency anemia in adolescents who present with heavy menstrual bleeding. J Pediatr Adolesc Gynecol 30:247–250
98. Tunnessen WW Jr, Oski FA (1987) Consequences of starting whole cow milk at 6 months of age. J Pediatr 111:813–816
99. Ziegler EE, Fomon SJ, Nelson SE, Rebouche CJ, Edwards BB, Rogers RR, Lehman LJ (1990) Cow milk feeding in infancy: further observations on blood loss from the gastrointestinal tract. J Pediatr 116:11–18
100. Yasa B, Agaoglu L, Unuvar E (2011) Efficacy, tolerability, and acceptability of iron hydroxide polymaltose complex versus ferrous sulfate: a randomized trial in pediatric patients with iron deficiency anemia. Int J Pediatr 2011:524520
101. Geisser P (2007) Safety and efficacy of iron(III)-hydroxide polymaltose complex. Arzneimittel-Forschung (Drug Research) 57:439–452
102. Powers JM, Buchanan GR, Adix L, Zhang S, Gao A, McCavit TL (2017) Effect of low-dose ferrous sulfate vs iron polysaccharide complex on hemoglobin concentration in young children with nutritional iron-deficiency anemia: a randomized clinical trial. JAMA 317:2297–2304
103. Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, Melse-Boonstra A, Brittenham G, Swinkels DW, Zimmermann MB (2015) Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood 126:1981–1989
104. Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, Moretti D, Zimmermann MB (2017) Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol 4:e524–e533
105. Stoffel NU, Zeder C, Brittenham GM, Moretti D, Zimmermann MB (2019) Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women. Haematologica:haematol 2019:220830
106. Litton E, Xiao J, Ho KM (2013) Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ 347:f4822
107. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J (2004) On the relative safety of parenteral iron formulations. Nephrol Dial Transplant 19:1571–1575
108. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J (2006) Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 21:378–382
109. Ng O, Keeler BD, Mishra A, Simpson JA, Neal K, Al-Hassi HO, Brookes MJ, Acheson AG (2019) Iron therapy for preoperative anaemia. Cochrane Database Syst Rev 12:CD011588
110. Harris RE, Garrick V, Curtis L, Russell RK (2018) Skin staining due to intravenous iron extravasation in a teenager with Crohn's disease. Arch Dis Child archdischild-2018-316405
111. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG (2005) Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol 16: 3070–3080
112. Feldman HI, Joffe M, Robinson B, Knauss J, Cizman B, Guo W, Franklin-Becker E, Faich G (2004) Administration of parenteral iron and mortality among hemodialysis patients. J Am Soc Nephrol 15:1623–1632
113. Hoen B, Paul-Dauphin A, Kessler M (2002) Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients. Clin Nephrol 57:457–461
114. Wuillemin WA, Krähenbühl S (2010) Hohe Ferritinwerte nach Eiseninfusion - gefährlich? Swiss Med Forum 10:844–846
115. Mantadakis E (2016) Advances in pediatric intravenous iron therapy. Pediatr Blood Cancer 63:11–16
116. Powers JM, McCavit TL, Buchanan GR (2015) Management of iron deficiency anemia: a survey of pediatric hematology/oncology specialists. Pediatr Blood Cancer 62:842–846
117. Boucher AA, Pfeiffer A, Bedel A, Young J, McGann PT (2018) Utilization trends and safety of intravenous iron replacement in pediatric specialty care: a large retrospective cohort study. Pediatr Blood Cancer 65:e26995
118. Dortschy R, Schaffrath Rosario A, Scheidt-Nave C, Thamm M, Gutsche J, Markert A (2009) Bevölkerungsbezogene Verteilungswerte ausgewählter Laborparameter aus der Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS). Gesundheitsberichterstattung des Bundes, Robert-Koch-Institut, Berlin
119. Kurth B-M (2007) Der Kinder- und Jugendgesundheitssurvey (KiGGS): Ein Überblick über Planung, Durchführung und Ergebnisse unter Berücksichtigung von Aspekten eines Qualitätsmanagements. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 50:533–546
120. Rampton D, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, Patni S, Szebeni J, Weiss G (2014) Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. Haematologica 99:1671–1676
121. Powers JM, O'Brien SH (2019) How I approach iron deficiency with and without anemia. Pediatr Blood Cancer 66:e27544
122. Stein RE, Plantz K, Maxwell EC, Mamula P, Baldassano RN (2018) Intravenous iron sucrose for treatment of iron deficiency anemia in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 66:e51–e55
123. Carvalho FSG, de Medeiros IA, Antunes H (2017) Prevalence of iron deficiency anemia and iron deficiency in a pediatric population with inflammatory bowel disease. Scand J Gastroenterol 52: 1099–1103
124. Danko I (2016) Response of iron deficiency anemia to intravenous iron sucrose in pediatric inflammatory bowel disease. J Pediatr Pharmacol Therap 21:162–168
125. Danko I, Weidkamp M (2016) Correction of iron deficiency anemia with intravenous iron sucrose in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 63:e107–e111
126. Valerio de Azevedo S, Maltez C, Lopes AI (2017) Pediatric Crohn's disease, iron deficiency anemia and intravenous iron treatment: a follow-up study. Scand J Gastroenterol 52:29–33
127. Carman N, Muir R, Lewindon P (2019) Ferric carboxymaltose in the treatment of iron deficiency in pediatric inflammatory bowel disease. Transl Pediatr 8:28–34
128. Papadopoulos M, Patel D, Korologou-Linden R, Goto E, Soondrum K, Fell JME, Epstein J (2018) Safety and efficacy of parenteral iron in children with inflammatory bowel disease. Br J Clin Pharmacol 84:694–699
129. Kaskel FJ (2006) Safety and efficacy of sodium ferric gluconate complex in iron-deficient pediatric hemodialysis patients. Nat Clin Pract Nephrol 2:244–245

130. Leijn E, Monnens LA, Cornelissen EA (2004) Intravenous iron supplementation in children on hemodialysis. J Nephrol 17:423–426
131. Ratcliffe LE, Thomas W, Glen J, Padhi S, Pordes BA, Wonderling D, Connell R, Stephens S, Mikhail AI, Fogarty DG, Cooper JK, Dring B, Devonald MA, Brown C, Thomas ME (2016) Diagnosis and management of iron deficiency in CKD: a summary of the NICE guideline recommendations and their rationale. Am J Kidney Dis 67:548–558
132. Warady BA, Kausz A, Lerner G, Brewer ED, Chadha V, Brugnara C, Dahl NV, Watkins SL (2004) Iron therapy in the pediatric hemodialysis population. Pediatr Nephrol (Berlin, Germany) 19: 655–661
133. Warady BA, Zobrist RH, Finan E, Ferrlecit Pediatric Study G (2006) Sodium ferric gluconate complex maintenance therapy in children on hemodialysis. Pediatr Nephrol (Berlin, Germany) 21: 553–560
134. Warady BA, Zobrist RH, Wu J, Finan E, Ferrlecit Pediatric Study G (2005) Sodium ferric gluconate complex therapy in anemic children on hemodialysis. Pediatr Nephrol (Berlin, Germany) 20: 1320–1327
135. Morgan HE, Holt RC, Jones CA, Judd BA (2007) Intravenous iron treatment in paediatric chronic kidney disease patients not on erythropoietin. Pediatr Nephrol (Berlin, Germany) 22:1963–1965
136. Gillespie RS, Symons JM (2005) Sodium ferric gluconate for post-transplant anemia in pediatric and young adult renal transplant recipients. Pediatr Transplant 9:43–46
137. Goldstein SL, Morris D, Warady BA (2013) Comparison of the safety and efficacy of 3 iron sucrose iron maintenance regimens in children, adolescents, and young adults with CKD: a randomized controlled trial. Am J Kidney Dis 61:588–597
138. Yorgin P (2005) Intravenous iron therapy in pediatric transplant recipients: what do we really know? Pediatr Transplant 9:1–3
139. Anbu AT, Kemp T, O'Donnell K, Smith PA, Bradbury MG (2005) Low incidence of adverse events following 90-minute and 3-minute infusions of intravenous iron sucrose in children on erythropoietin. Acta Paediatr 94:1738–1741
140. DelRosso L, Bruni O (2019) Treatment of pediatric restless legs syndrome. Adv Pharmacol (San Diego, CA) 84:237–253
141. Grim K, Lee B, Sung AY, Kotagal S (2013) Treatment of childhood-onset restless legs syndrome and periodic limb movement disorder using intravenous iron sucrose. Sleep Med 14: 1100–1104
142. Auerbach M (2011) Should intravenous iron be upfront therapy for iron deficiency anemia? Pediatr Blood Cancer 56:511–512
143. Mantadakis E (2018) Intravenous iron: safe and underutilized in children. Pediatr Blood Cancer 65:e27016
144. Crary SE, Hall K, Buchanan GR (2011) Intravenous iron sucrose for children with iron deficiency failing to respond to oral iron therapy. Pediatr Blood Cancer 56:615–619
145. Powers JM, Shamoun M, McCavit TL, Adix L, Buchanan GR (2017) Intravenous ferric carboxymaltose in children with iron deficiency anemia who respond poorly to oral iron. J Pediatr 180:212–216
146. Mantadakis E, Roganovic J (2017) Safety and efficacy of ferric carboxymaltose in children and adolescents with iron deficiency anemia. J Pediatr 184:241
147. Mantadakis E, Tsouvala E, Xanthopoulou V, Chatzimichael A (2016) Intravenous iron sucrose for children with iron deficiency anemia: a single institution study. World J Pediatr 12:109–113
148. Pinsk V, Levy J, Moser A, Yerushalmi B, Kapelushnik J (2008) Efficacy and safety of intravenous iron sucrose therapy in a group of children with iron deficiency anemia. Israel Med Assoc J 10: 335–338
149. Plummer ES, Crary SE, McCavit TL, Buchanan GR (2013) Intravenous low molecular weight iron dextran in children with iron deficiency anemia unresponsive to oral iron. Pediatr Blood Cancer 60:1747–1752
150. Tan MLN, Windscheif PM, Thornton G, Gaynor E, Rodrigues A, Howarth L (2017) Retrospective review of effectiveness and safety of intravenous ferric carboxymaltose given to children with iron deficiency anaemia in one UK tertiary centre. Eur J Pediatr 176: 1419–1423
151. Akarsu S, Taskin E, Yilmaz E, Yilmaz H, Kilic M, Aygun AD (2006) Treatment of iron deficiency anemia with intravenous iron preparations. Acta Haematol 116:51–57
152. Clenin G, Cordes M, Huber A, Schumacher YO, Noack P, Scales J, Kriemler S (2015) Iron deficiency in sports - definition, influence on performance and therapy. Swiss Med Wkly 145:w14196
153. Rao R, Georgieff MK (2009) Iron therapy for preterm infants. Clin Perinatol 36:27–42
154. Akin M, Atay E, Oztekin O, Karadeniz C, Karakus YT, Yilmaz B, Erdogan F (2014) Responsiveness to parenteral iron therapy in children with oral iron-refractory iron-deficiency anemia. Pediatr Hematol Oncol 31:57–61
155. Akin M, Sarbay H, Guler S, Balci YI, Polat A (2016) Response to parenteral iron therapy distinguish unexplained refractory iron deficiency anemia from iron-refractory iron deficiency anemia. Int J Lab Hematol 38:167–171
156. Giger M, Achermann R (2013) Iron substitution in outpatients in Switzerland: increase of costs associated with intravenous administration. Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen 107:320–326