Review

Parenteral Iron Therapy for Pediatric Patients

Elpis Mantadakis * [ID]**, Sonia Alexiadou and Panagiota Zikidou**

Department of Pediatrics, Hematology/Oncology Unit, University General Hospital of Alexandroupolis,
68 100 Alexandroupolis, Greece; s.alexiadou@hotmail.com (S.A.); pzikidou@yahoo.gr (P.Z.)
* Correspondence: emantada@med.duth.gr

Abstract: Iron deficiency (ID) is by far the most common nutritional disorder in developing and developed countries. When left untreated, ID leads to anemia. Although the usually recommended treatment for iron deficiency anemia (IDA) is oral iron therapy with countless products, such therapy necessitates administration for >3–6 months with questionable patient compliance since most oral iron products have an unpleasant metallic aftertaste and cause intestinal side effects. In addition, in certain gastrointestinal conditions, such as inflammatory bowel diseases or untreated gluten-sensitive enteropathy, oral iron therapy is contraindicated or unsuccessful. Intravenous iron is considered safe in adults, where adverse events are mild and easily managed. The experience with parenteral iron in children is much more limited, and many pediatricians appear reluctant to use it because of uncorroborated fears of serious anaphylactic reactions. In the current article, we thoroughly review the available pediatric literature on the use of all commercially available parenteral iron products except ferumoxytol, which was recently removed from the market. We conclude that parenteral iron appears to be safe in children; it works faster than oral iron, and the newer third-generation products allow replacement of the total iron deficit in a single sitting.

Keywords: iron deficiency; iron deficiency anemia; intravenous iron; iron sucrose; ferric carboxymaltose; iron isomaltoside; inflammatory bowel diseases

1. Introduction

Iron deficiency anemia (IDA) is the most common hematologic condition in children and adolescents worldwide [1,2], and limited evidence shows substantial variability in its management. A 20-question electronic survey that solicited responses to a hypothetical case of nutritional IDA in a toddler by members of the American Society of Pediatric Hematology/Oncology showed that most respondents would prescribe oral ferrous sulfate (84%) [3]. For an adolescent with heavy menstrual bleeding and IDA, most physicians recommended oral ferrous sulfate (83%). For IDA refractory to oral treatment, intravenous iron therapy was recommended most frequently, with 48% recommending iron sucrose (IS), 17% recommending ferric gluconate, and 15% recommending low-molecular-weight iron dextran (LMWID) [3].

Oral iron therapy has serious limitations which include poor absorption and non-adherence due to frequent gastrointestinal side effects [4]. Moreover, IDA is very common in the setting of inflammatory bowel diseases (IBD), especially in children. It is a frequent cause of hospitalization in these patients, and it prevents physicians from discharging hospitalized patients and impacts disease progression and healthcare resource utilization [5].

Quality improvement methods can improve screening rates for ID and IDA. In a single-institution study, among 232 patients with newly diagnosed IBD, 88% met the criteria for IDA or isolated ID [6]. Interestingly, rates of ID/IDA screening increased significantly from a baseline of 20% to >90% after implementation of quality improvement methods. In a study of newly diagnosed IBD patients followed prospectively for one year following diagnosis in 29 European and 1 Australian center, 42% of patients had at least one instance of anemia, and although most patients were assessed for anemia regularly, a full anemia

work-up was often overlooked [7]. Stein et al. evaluated the routine practice management of anemia in patients with IBD across nine European countries [8]. Gastroenterologists were surveyed about their last five IBD patients treated for anemia. Anemia and iron status were mainly assessed through hemoglobin (88%) and serum ferritin (75%). Transferrin saturation was only tested in 25% of patients. At diagnosis of anemia, 56% presented with at least moderate anemia (Hb < 10 g/dL) and 15% with severe anemia (Hb < 8 g/dL). ID defined as ferritin <30 ng/mL was detected in 76% of patients. Almost all patients (92%) received iron supplementation; however, only 28% received intravenous iron and 67% oral iron [8]. Hence, most IBD patients received oral iron even though this route may exacerbate their disease, and despite international guidelines recommending intravenous iron as the preferred therapeutic option [8–11]. Table 1 shows indications for pediatric intravenous iron therapy, while Table 2 compares oral and intravenous iron therapy.

Table 1. Indications for administration of intravenous iron in pediatric patients.

Inability to swallow oral iron preparations
Failure of oral iron therapy (poor compliance due to taste, adverse effects usually from the digestive system, need for long-term treatment, etc.)
Inadequate absorption of iron from the gut (e.g., celiac disease, IBD, short bowel syndrome, gastric bypass surgery, iron-refractory iron deficiency anemia (IRIDA), etc.)
Continued blood loss from the digestive tract (e.g., esophageal varices, intestinal mucosal telangiectasias, etc.)
Need for rapid correction of anemia (e.g., before elective surgery)
Functional IDA (e.g., chronic renal failure, rheumatoid arthritis, etc.)
Refusal of transfusions for religious or other reasons

Table 2. Comparison of oral and intravenous iron therapy.

Side Effects	Duration of Therapy	Cost	Quality of Life
Gastrointestinal	At least 3 months	Low, but the need for laboratory and clinical follow-up increases cost	It depends on patient compliance, anemia correction, and follow-up visits for clinical and laboratory work-up
Infusional	Correction of the total iron deficit with a single or a few infusions	High, due to the acquisition cost of parenteral iron	Outpatient or inpatient administration, frequently only once

2. History of Intravenous Iron Therapy

In 1964, Marchasin and Wallerstein were the first to publish results of intravenous iron administration in large doses, i.e., 1–3 g, as high-molecular-weight iron dextran (HMWID) (Imferon®) in 37 patients with IDA and 8 patients with acute gastrointestinal bleeding [12]. The methodology of patient selection was not well described; all patients responded, but one experienced a delayed reaction, i.e., fever with chills without hypotension or wheezing. The first prospective study on the use of intravenous iron was published in 1980 in 471 patients, again with Imferon® [13]. All patients responded, but three developed signs of anaphylaxis, including respiratory arrest and hypotension. Imferon® was eventually withdrawn from the market in 1991 and replaced by another HMWID product, Dexferrum®, in 1996. This product was also withdrawn from the market in 2014 after Chertow et al. documented that most severe adverse drug events (ADEs) due to intravenous iron administration were caused by this HMWID formulation [14,15]. In the last 20 years, the development of third-generation parenteral iron preparations has made it possible to correct safely large iron deficits with a single intravenous infusion (total dose infusion,

TDI). In the remaining text, we will focus on the use of parenteral iron in pediatric patients outside of the setting of chronic kidney disease.

3. Intravenous Iron Formulations

All intravenous iron products are iron-carbohydrate complexes consisting of a mineral core surrounded by a carbohydrate moiety that is intended to stabilize the complex [16]. A first-generation intravenous iron product was HMWID, which, as previously said, is not commercially available anymore. HMWID was very effective in correcting IDA in both adults and children but was associated with serious hypersensitivity reactions (HSRs) that were occasionally fatal [15].

In 1981, Halpin et al. were the first to report the use of HMWID in six children with severe IBD and IDA [17]. All were given a single TDI after a taper of the parenteral nutrition, and all had laboratory and clinical evidence of improvement in their anemia. Mamula et al. administered 119 TDI of HMWID in 70 pediatric patients with IBD, i.e., 20 with ulcerative colitis and 50 with Crohn's disease [18]. The average increase in hemoglobin concentration was 2.9 g/dL. Eleven immediate HSRs developed in 10 patients (9% of the total number of infusions).

The second-generation intravenous iron products include LMWID, ferrous gluconate, and IS, also known as sucroferric oxyhydroxide or iron saccharate. LMWID has a good safety profile that is comparable to other newer parenteral iron products [19]. IS continues to be the most widely used parenteral iron product worldwide, with an excellent safety record, provided that single daily doses do not exceed 300 mg and that administration is performed using slow infusion ($\geq$90 min) [20]. In case a large iron deficit needs correction, repeated doses every other day are required to minimize the production of labile-free iron that has been shown to be etiologically related to HSRs [21].

The third-generation intravenous iron products include ferumoxytol, which is not commercially available anymore and will not be discussed further, ferric carboxymaltose (FCM), and iron isomaltoside 1000 (IIM), also known as ferric derisomaltose in the US.

Prior to intravenous iron administration, the total body iron deficit should be calculated in patients with IDA. This is usually determined using the following Ganzoni formula: [Body weight (kg) $\times$ (target hemoglobin–actual hemoglobin (in g/L) $\times$ 0.24] + iron depot (mg), where iron depot for <35 kg body weight is 15 mg/kg, and for $\geq$35 kg, body weight is 500 mg [22,23]. Table 3 shows all available iron products for intravenous administration.

Table 3. Parenteral iron products. Note that HMWID and ferumoxytol are not commercially available anymore.

First-generation products	High-molecular-weight iron dextran (HMWID)
Second-generation products	Low-molecular-weight iron dextran (LMWID), ferric gluconate, iron sucrose (sucroferric oxyhydroxide or iron saccharate)
Third-generation products	Ferumoxytol, ferric carboxymaltose, iron isomaltoside 1000 (ferric derisomaltose in the US)

4. Safety of Intravenous Iron

Rapid release of iron from intravenous iron preparations can saturate the iron transport system, resulting in oxidative stress with adverse clinical consequences [16]. The reactivity of intravenous iron complexes correlates inversely with their molecular weight, i.e., larger complexes are less prone to release large amounts of labile-free iron [16]. Type I complexes, such as iron dextran preparations or FCM, have a high molecular weight and deliver iron from the complex to transferrin in a regulated way via macrophage endocytosis and coordinated export. Such complexes are clinically well-tolerated even at high intravenous doses. Type II complexes such as IS release larger amounts of weakly bound iron in the blood. Despite their lower molecular weight and weaker stability, they are appropriate for intravenous administration, but the recommended highest single doses are considerably

lower, and the administration times are substantially longer compared to type I compounds. Type III and IV complexes like sodium ferric gluconate have variable amounts of low-molecular-weight components and are likely to generate large amounts of non-transferrin-bound iron prohibiting the administration of large doses of iron in a single visit. For example, the maximum approved daily dose of ferric gluconate is only 125 mg (1.5 mg/kg of elemental iron for children up to the maximum adult daily dose of 125 mg).

Avni et al. performed an exhaustive systematic review and meta-analysis of all randomized clinical trials published until 1 January 2014 that compared intravenous iron to oral iron, no iron, or placebo for the occurrence of severe ADEs [24]. The secondary outcomes studied were all-cause mortality and other adverse events. A total of 103 trials published since 1965 were included. All studies included adults only. A total of 10,390 patients were treated with intravenous iron compared with 4044 patients treated with oral iron, 1329 with no iron, and 3335 with placebo. There was no increased risk of severe ADEs with intravenous iron (relative risk 1.04).

Iron is a pro-oxidant, an important nutrient for many bacteria, and has been shown to exacerbate sepsis in laboratory animals [25,26]. Consequently, concerns have been raised that intravenous iron might increase oxidative stress, infections, mortality, or even tumor growth. Despite these concerns, no study so far has shown an increased infectious risk with the administration of parenteral iron, something confirmed in the meta-analysis of Avni et al. [24].

Acute onset myalgia and/or arthralgia and/or flushing may occur with any parenteral iron formulation. In these cases, there is no increase in serum tryptase levels, a serologic marker for anaphylaxis [19]. Based on a validated tool of labile iron, the ferrozine-detectable iron, the amount of labile iron is highest with ferric gluconate and IS, lower with LMWID, and lowest with FCM and IIM. Notably, systematic premedication with antihistamines, corticosteroids, and leukotriene antagonists is not routinely recommended with intravenous iron to avoid vasoactive reactions that could be misinterpreted as causally related to intravenous iron [27]. In any case, iron infusions should be meticulously observed, and, in the event of an HSR, recognition and management should be fast [28].

Most reactions to intravenous iron are minor systemic reactions to the labile iron that resolve spontaneously and rarely recur with rechallenge. Acute HSRs during iron infusions are very rare but can be life-threatening. Complement activation-related pseudo-allergy (CARPA) triggered by iron nanoparticles is likely the most frequent pathogenetic mechanism in acute reactions [21], although an immunological IgE-mediated response may be involved in rare cases. Major risk factors for an HSR include a previous reaction to a parenteral iron product, a history of multiple drug allergies or severe atopy, a fast infusion rate, and possibly an underlying systemic inflammatory disease [28]. Since most reporting systems for ADEs are voluntary, passive, and do not include causality assessment, the incidence of intravenous iron-related ADEs cannot be objectively estimated. Adequately powered direct comparisons of different forms of intravenous iron are required to assess their safety.

Szebeni et al. have reviewed the available evidence for HSRs to intravenous iron and its therapeutic management [29]. They concluded that current therapeutic protocols remain non-specific due to the use of non-evidence-based empirical measures (antihistamines, corticosteroids, adrenaline) which neglect the fact that most intravenous iron reactions are not IgE-mediated anaphylactic reactions. A new approach is suggested based on the assumption that intravenous iron reactions largely represent CARPA. More specifically, labile iron activates the complement system which leads to the formation of anaphylatoxins. The serum concentration of the latter is the result of cellular uptake and metabolism by carboxypeptidases, and they can trigger mast cell activation. Slower administrations are less reactogenic, and modern administration protocols for intravenous iron are based on slower infusions [28].

A retrospective new user cohort study of adult intravenous iron recipients enrolled in the US fee-for-service non-dialysis Medicare program described a total of 274 anaphylaxis

cases at first exposure to intravenous iron with an additional 170 cases identified during subsequent administrations [30]. The risk for anaphylaxis at first exposure was 68 per 100,000 persons for iron dextran and 24 per 100,000 persons for all non-dextran intravenous iron products combined (IS, iron gluconate, and ferumoxytol), for an adjusted odds ratio of 2.6. The estimated cumulative anaphylaxis risk following a TDI of 1000 mg iron administered within a 12-week period was highest with iron dextran (82 per 100,000 persons) and lowest with IS (21 per 100,000 persons).

In a single-center Dutch study, every HSR associated with the administration of intravenous iron in adults was prospectively classified using the Ring and Messmer classification [31]. HSRs occurred in 2.1% of 836 infusions of FCM, and in 8.7% of 496 infusions of IIM. Regardless of the type of intravenous iron, patients with comorbidities had a 3.6-fold higher risk of HSRs.

These results have not been replicated by others. Pollock and Biggar reviewed 21 prospective studies including over 8000 patients who received IIM, FCM, or IS. By using the standardized Medical Dictionary for Regulatory Activities queries to compare the safety of these three intravenous iron products, they showed the risk of severe HSRs to be lower with IIM relative to FCM and IS [32].

Although the risk of HSRs is widely believed to be lower with FCM than with iron dextran because of its non-dextran carbohydrate moiety, there are recent studies that do not support this assumption. A retrospective pharmacoepidemiologic study with a case-population design estimated the HSRs to intravenous iron using IQVIA^{TM} sales data [33]. The spontaneously reported HSRs were retrieved from the WHO database (VigiBase^{TM}) using various search criteria. HMWID and LMWID were grouped together. The relative risk for FCM versus iron dextran was 4.18 for standardized MedDRA$^®$ Query anaphylactic reaction, 12.9 for type I-IV HSRs, 1.72 for anaphylactic/anaphylactoid reactions, and 1.92 for death. Thus, the risk of spontaneously reported HSR was consistently higher with FCM than with iron dextran, something that does not support that dextran-free intravenous irons are associated with fewer HSRs [33]. However, it should be noted that this may be the result of a Weber effect, a well-known reporting bias in pharmacovigilance studies [34]. Briefly, the passive reporting of adverse effects after regulatory approval of a drug peaks at the end of the second year after approval and declines steadily thereafter. Physicians may be more inclined to report HSRs of FCM, which is a newer product on the market compared to LMWID, which has been on the market for several decades.

Nathell et al. performed a retrospective pharmacoepidemiologic study with a case-population design for the adverse events of intravenous iron products including HSRs for the 4-year periods before and after the implementation of risk minimization measures for intravenous iron in Europe [35]. Information was obtained from the safety surveillance database of spontaneously reported severe HSRs EudraVigilance, while exposure was estimated using IQVIA MIDAS sales data in the countries of the European economic area. Reporting rates for severe HSRs for individual products were heterogeneous. Reporting rates were low for IS and ferric gluconate, and higher at the beginning and lower at the end of the study period for FCM. No clear trend was detected for LMWID and IIM [35].

The relatively limited safety data of parenteral iron products in pediatric patients are summarized under each formulation. In general, all products appear safe provided that the preparation and administration guidelines are meticulously followed.

5. Low-Molecular-Weight Iron Dextran (LMWID)

The manufacturer of LMWID recommends a test dose prior to administration, although an uneventful test dose does not ensure that an anaphylactic reaction will not occur. Plummer et al. at Children's Medical Center of Dallas administered intravenous LMWID in children with ID in whom oral iron was ineffective [36]. LMWID was administered as a TDI over 60 min in an outpatient setting. A total of 31 patients aged 11 months to 18 years received therapy, and 24 were evaluable for response. Median hemoglobin increments were 3.5, 1.9, and 1.8 g/dL in patients with IDA due to poor nutrition, chronic blood loss,

and miscellaneous causes, respectively. Two-thirds of evaluable patients had a complete hematologic response. Twenty-nine percent of the patients had mild non-specific ADEs upon initiation of the LMWID infusion [36]. Boucher et al. reviewed the use of LMWID at a tertiary children's hospital in the US [37]. Overall, 254 infusions in 191 patients aged 0.7–20.9 years were studied. Premedication was administered prior to one-fourth of the infusions, while all patients received a test dose. LMWID replaced at least 75% of the estimated iron deficit in a single infusion for 76% of patients. The mean hemoglobin and ferritin increases were 2.1 g/dL and >100 ng/mL, respectively. Infusion-related adverse events were rare, occurring in only 4.7% of infusions and 67% during the test dose. All resolved quickly and completely without sequelae. It is of note that no ADEs occurred in children <10 years of age [37].

6. Iron Sucrose (IS)

Iron sucrose (IS) is very safe and effective, but for safety reasons, its maximum weekly dose should not exceed 600 mg. Surico et al. in Bari, Italy, were one of the first to administer intramuscular or intravenous IS in 33 children with severe ID and/or IDA who failed to respond to oral iron supplementation [38]. All children showed recovery from IDA, with similar improvement in hemoglobin between the two routes, but the duration of treatment was longer with intramuscular injections. Michaud et al. at the Children's Hospital of Lille, France, administered IS to 22 infants and children aged 5 months to 17 years with IDA on long-term parenteral nutrition [39]. Each patient received a test dose of 25 mg of IS prior to the infusion. IS was well tolerated except in one patient who developed a transient rash and hypotension after completion of the last IS infusion. Intravenous iron led to a significant increase in hemoglobin concentration of 2.2 g/dL within 45 days (range 0.4–4.3 g/dL). In a study from Israel of 45 children aged 11 months to 16 years failing oral iron therapy, intravenous IS was administered at a daily dose of 5 mg/kg/day three times per week until the total calculated iron deficit was reached [40]. Out of 45 patients, 44 were non-compliant with oral iron, 9 had *Helicobacter pylori* gastritis, and 16 suffered from intestinal malabsorption of various etiologies. The mean hemoglobin prior to therapy was 7.43 g/dL and increased to 9.27 g/dL within 14 days after treatment and to 12.4 g/dL, 6 months later. The only recorded side effect was an episode of temporary and reversible hypotension. Crary et al. described 38 children who received a total of 510 doses of IS for non-renal reasons [41]. There were only six adverse reactions, while patients in all categories had a good response with a median hemoglobin rise of 1.9–3.1 g/dL depending on the indication. We administered IS to 12 children (6 females) aged 1.2–14 years (median age 8.9 years) with IDA of various etiologies [42]. IS infusions were given on alternate days up to three times per week. IS was effective in raising hemoglobin to normal in all patients, i.e., from 7.6 ± 2.38 g/dL to 12.4 ± 0.64 g/dL, within 31–42 days after the first infusion. Injection site reactions in three cases and transient taste perversion in one case were the only side effects. In a retrospective study, Kaneva et al. reviewed all IS administrations at Los Angeles Children's Hospital over a 10-year period [43]. A total of 142 children received IS, with a mean age of 11.75 years. Only one patient developed cough and wheezing during the infusion, while no other adverse effects were recorded. Intravenous IS led to a considerable improvement in iron studies and a clinically meaningful increase in hemoglobin.

Sharma et al. performed a prospective clinical trial of post-menarchal adolescent females with ID with or without mild anemia and fatigue who received a standardized regimen of IS [44]. Treatment was well tolerated, and patients demonstrated a sustained increase in ferritin at 6 weeks and at 6 months after the infusions. By using a standardized fatigue scale, they demonstrated a clinically significant improvement in the reported patient and parent fatigue scores supporting the non-hematological functions of iron in reducing fatigue [45]. Sabe et al. reviewed the medical records of IBD patients <22 years of age who received intravenous IS [46]. Overall, 88 patients were identified, 52 with Crohn's disease, 33 with ulcerative colitis, and 3 with unclassified IBD. They received 329 infusions of IS over 121 courses. Six patients developed minor adverse reactions, while no patients developed anaphylaxis. There was a

highly significant rise in hemoglobin of 2.8 g/dL from a mean baseline value of 9.1 ±1.4 to 11.9 ± 1.8 g/dL after treatment. Finally, a single-institution study of 16 children with restless leg syndrome/periodic limb movement disorder who received IS was published [47]. Side effects were minor and transient. There was improved sleep in 10 patients, no improvement in two, while no follow-up was available for four subjects.

7. Ferric Carboxymaltose (FCM)

FCM has been extensively studied in adults, [48] where it prevents the recurrence of anemia in patients with IBD, compared with placebo [49]. It also has better efficacy and compliance with a good safety profile, compared with IS [50]. Table 4 shows the recommended dose of FCM based on hemoglobin and patient body weight.

Table 4. Recommended doses of FCM for IV administration based on patient's pre-treatment hemoglobin and body weight.

Hemoglobin	Patient Body Weight		
g/dL	<35 kg	35–70 kg	≥70 kg
<10	30 mg/kg	1500 mg	2000 mg
10–14	15 mg/kg	1000 mg	1500 mg
≥14	15 mg/kg	500 mg	500 mg

NCT03523117 was a multicenter randomized active-controlled study to investigate the efficacy and safety of FCM in pediatric patients with IDA. Randomization was stratified by baseline hemoglobin (<10, ≥10 g/dL) and age (1 to <12 years, and ≥12 to 17 years). A 1:1 randomization took place with participants receiving FCM or oral ferrous sulfate. Overall, 40 patients (1–12 years, 10 patients; 12–17 years, 30 patients) received FCM: 15 mg/kg up to 750 mg on days 0 and 7 for a total dose of 1500 mg. The median age of patients who received FCM was 14.5 years. ADEs that occurred in ≥4% of patients who received FCM were hypophosphatemia (13%), local infusion reactions (8%), rash (8%), headaches (5%), and vomiting (5%). Based on this study, FCM gained approval in the US on 16 December 2021, for use in children with IDA over 1 year of age, and a similar approval followed in Europe.

Powers et al. at Children's Medical Center of Dallas assessed in a retrospective cohort study all FCM infusions administered in children with IDA over a 12-month period [51]. A total of 116 FCM infusions were administered to 72 patients with IDA refractory to oral iron treatment (median age, 13.7 years; range, 9 months to 18 years). Median pre-infusion and post-infusion hemoglobin values were 9.1 g/dL and 12.3 g/dL, respectively, at 4–12 weeks after the initial infusion. Sixty-five patients (84%) experienced no adverse effects. Minor transient complications were encountered during or immediately after seven infusions. Mantadakis and Roganovic assessed a total of 27 FCM infusions in children and adolescents with IDA [52]. Thirteen patients had failed previous oral iron therapy, and all had pretreatment serum ferritin <12 ng/mL. The median pretreatment hemoglobin was 7.3 g/dL and rose to 12.6 g/dL at >4 weeks after the initial FCM infusion. No case of urticaria, pruritus, or wheezing occurred.

A Dutch multicenter study tested whether intravenous or oral iron supplementation is superior in improving physical fitness in 64 anemic children with IBD [53]. Children aged 8–18 years with IBD and anemia defined as hemoglobin z-score < 2 were randomly assigned to a single dose of FCM (33 children) or 12 weeks of oral ferrous fumarate (31 children). The primary endpoint was a change in the 6-min walking distance (6MWD) from baseline, expressed as z-score, while the secondary outcome was the change in Hb z-score compared to pretreatment values. One month after the start of iron therapy, the 6MWD z-score of patients in the FCM group had increased by 0.71 compared with 0.11 in the oral group, a significant difference validating that a single dose of FCM is superior to oral ferrous fumarate with respect to quick improvement of physical fitness [53].

In a single-center observational cohort study of 23 children with intestinal failure, mostly due to short gut syndrome requiring ongoing intravenous iron supplementation, patients were transitioned from IS to FCM [54]. Sixteen patients received IS and later switched to FCM; five received IS only; and two received FCM only. Both forms of intravenous iron were effective. However, the median number of infusions over 12 months for those taking IS was significantly higher (15 vs. 2).

Korczowski et al. completed a phase 2, non-randomized, multicenter study of the safety profile and appropriate dosing of FCM in 35 children and adolescents with IDA [55]. Enrolled patients were 1–17 years old, with hemoglobin <11 g/dL, transferrin saturation <20%, and received single doses of FCM 7.5 mg/kg (n = 16) or 15 mg/kg (n = 19). FCM was well tolerated; urticaria was the most common drug-related adverse event. Systemic exposure to iron increased in a dose-dependent manner with an approximate doubling of mean baseline-corrected maximum serum iron concentration and area under the serum concentration-time curve. Baseline hemoglobin was 9.2 in the FCM 7.5 mg/kg and 9.5 g/dL in the 15 mg/kg groups, respectively, with mean maximum changes in hemoglobin of 2.2 and 3.0 g/dL, respectively. Hence, 15 mg/kg of FCM appears to be more effective in correcting IDA in children [55].

Laass et al. in Dresden, Germany, treated 72 patients from 0 to 18 years old with underlying gastrointestinal disorders and concomitant IDA with FCM [56]. Most patients had Crohn's disease (40.3%) or ulcerative colitis (30.5%). Overall, 147 infusions of FCM infusions were given. Correction of IDA with a rise in hemoglobin from 9.5 g/dL at baseline to 11.9 g/dL within 5–12 weeks was noted. Interestingly, decreases in inflammatory markers were observed post-FCM, potentially suggesting reduced inflammation with iron repletion. Three subjects reported mild adverse drug reactions related to FCM likely due to the long duration of administration and the high volume of saline solution for dilution. Hence, the method of administration was amended to 60 min infusion time and dilution with ≤100 mL of saline solution.

A Cochrane Library systematic review of interventions for treating IDA in IBD that included both adults and children showed that intravenous FCM was more effective than IS for the resolution of anemia; however, due to the low number of studies in each comparison area and substantial clinical heterogeneity, it was unable to draw conclusions on which of the other treatments was most effective in IDA of IBD [57].

Aksan et al. reviewed 33 pediatric studies containing clinical data relating to FCM. Most studies were retrospective and included patients with various underlying conditions. They showed that FCM is an effective and well-tolerated treatment for ID/IDA in children and adolescents [58]. We treated 37 children with ID/IDA with FCM in four academic pediatric clinics in Northern Greece [59]. Overall, 41 FCM infusions were administered. All infusions were tolerated well. In addition, 11 articles reporting 1231 infusions of FCM in 866 children were reviewed by us. Among them, 52 (6%) children developed ADEs that were graded as mild or moderate (grades I–III) [59].

8. Iron Isomaltoside 1000 (IIM, Ferric Derisomaltose in the US)

The efficacy and safety of IIM in routine care of IBD patients with IDA was assessed by Stein et al., who treated 197 IBD adult patients in Germany [8]. Data were recorded at baseline and after 4, 8, and 16 weeks. Hemoglobin increased from 10.7 (±1.6) g/dL at baseline to 13.1 (±1.5) g/dL at the final visit. About 8% of the patients reported transient adverse reactions, most commonly nausea, vomiting, and skin reactions. There are no pediatric data on the use of IIM. NCT05179226 is a phase III, prospective, open-label, multicenter trial of IIM in children 0 to <18 years of age with IDA due to non-dialysis-dependent chronic kidney disease or with IDA who are intolerant or unresponsive to oral iron. Overall, 200 children <18 years of age will receive 10 mg/kg or 20 mg/kg IIM for a maximum dose of 1000 mg. Twenty-four will have PK data collected, at seven or eight time points. Twelve children will receive 10 mg/kg, and the remaining 188 will receive 20 mg/kg. The study took off on 28 November 2022, and is scheduled for completion

on 30 April 2024. Table 5 describes instructions for safe intravenous administration of all parenteral iron products with pediatric indications.

Table 5. Dilution and administration guidelines of all commercially available parenteral iron products with pediatric indications.

	LMWID	Ferric Gluconate	Iron Sucrose	Ferric Carboxymaltose
Test dose recommended	Yes	No	No	No
TDI possible	Yes	No	No	Yes
Rate of IV administration	Over 60 min	Over 60 min	If dose ≤100 mg over ≥30 min If dose 100–200 mg over ≥60 min If dose 200–300 mg over ≥90 min Do not use single doses >300 mg	Dilute to ≥2 mg/mL over ≥15 min BW <50 kg: 5 mg/kg on day 1; repeat dose after at least 7 days (max: 1500 mg per course in the US) ≥50 kg: 750 mg on day 1; repeat dose after at least 7 days (max: 1500 mg per course in the US) In Europe, max 1000 mg/day, not to exceed 1000 mg/week
Iron concentration in commercially available vial	50 mg/mL	12.5 mg/mL	20 mg/ml	50 mg/mL
IV preparation guidelines	Dilute in sterile 0.9% NaCl and infuse over 4 to 6 h	Dilute in 100 mL of sterile 0.9% NaCl and infuse over 1 h	Dilute in sterile 0.9% NaCl. The final solution should be 1 mg/mL	Dilute up to 750 mg in ≤250 mL of 0.9% NaCl. The final solution must be ≥2 mg/mL

TDI: total dose infusion; BW: body weight.

9. Parenteral Iron-Induced Hypophosphatemia

Hypophosphatemia is a unique side effect of parenteral iron therapy. For unknown reasons, intravenous iron increases intact fibroblast growth factor 23 within a day of its administration followed by increased urinary phosphate excretion and decreased 1,25-dihydroxy-vitamin D and ionized calcium [60]. These latter changes precipitate secondary hyperparathyroidism that sustains hypophosphatemia and renal phosphate wasting even after normalization of intact fibroblast growth factor 23 [61,62]. Wolf et al. reported results of two identically designed, open-label, randomized clinical trials in 245 patients aged ≥ 18 years with IDA (hemoglobin ≤11 g/dL and serum ferritin level ≤100 ng/mL) and intolerance or unresponsiveness to ≥1 month of oral iron [63]. All patients were treated with intravenous iron as IIM, 1000 mg, on day 0, or FCM, 750 mg, on days 0 and 7. The primary endpoint was the incidence of hypophosphatemia defined as serum phosphate level <2 mg/dL between baseline and day 35. The incidence of hypophosphatemia was significantly lower following IIM vs. FCM (trial A: 7.9% vs. 75%; trial B: 8.1% vs. 73.7%).

Shaefer et al. completed a systematic literature search of 43 articles reporting outcomes on hypophosphatemia after intravenous FCM or IIM [64]. Hypophosphatemia rate and severity were compared after stratification for chronic kidney disease. FCM induced a significantly higher incidence of hypophosphatemia than IIM (47% vs. 4%), and significantly greater mean decreases in serum phosphate (0.40 vs. 0.06 mmol/L). Moreover, hypophosphatemia persisted at three months in up to 45% of patients treated with FCM. Meta-regression analysis identified low baseline serum ferritin and transferrin saturation and normal kidney function as significant predictors of hypophosphatemia [64].

Regarding the occurrence of hypophosphatemia with FCM administration in children, Posod et al. performed a retrospective, observational study at Innsbruck University Hospital in Austria [65]. Children were included if FCM was administered, and plasma phosphate concentrations were determined no longer than 6 months prior to and up to a year after the first infusion date. A total of 36 patients corresponding to 71 FCM doses were included. All children had normal baseline plasma phosphate concentrations. After the first FCM dose, hypophosphatemia occurred in 16.7% of the patients. Regarding all doses administered, hypophosphatemia occurred after 11.3% of FCM treatments.

Cococcioni et al. retrospectively assessed the rate of post-infusion hypophosphatemia in a cohort of children with IBD and IDA treated with FCM [66]. Overall, 128 patients were identified. A total of 83 children (64.8%) received a single infusion, while 45 children (35.2%) received repeated infusions; 25 children had low post-infusion serum phosphate, while 2 developed severe hypophosphatemia.

Finally, in the largest retrospective report of phosphorus serum level documentation in children, adolescents, and young adults ≤21 years old treated with FCM in routine clinical care, 313 FCM infusions were administered to 225 patients over 12 months at Texas Children's Hospital [67]. Most patients were female (62%) with a median age of 9.2 years. Hypophosphatemia occurred after 14% of the 313 infusions, administered in 40 patients. Of the patients who developed hypophosphatemia, none developed symptoms, while 18% were prescribed phosphorus supplements. Hence, FCM-induced hypophosphatemia appears to be less common in children compared to adults. More studies are needed to address the long-term clinical consequences of hypophosphatemia in children who received FCM for IDA.

10. Conclusions

The widespread belief that parenteral iron is best avoided in children with IDA unless severe malabsorption or a life-threatening condition is present is unsubstantiated. The newer parenteral iron products appear to be safe in pediatric patients; they work faster than oral iron and are convenient for patients who may prefer them over lengthy oral iron therapy. The latter has several unresolved issues, including what oral product to use, at what dose, in how many doses, etc. [68]. For all these reasons, the front-line use of intravenous iron will likely increase in the years to come for the treatment of moderate to severe IDA in children [69]. However, as the dilution and administration instructions differ substantially between different intravenous iron products, physicians should familiarize themselves with the preparation and dispensing guidelines in order to administer parenteral iron safely.

References

1. Mantadakis, E. Iron deficiency anemia in children residing in high and low-income countries: Risk factors, prevention, diagnosis and therapy. *Mediterr. J. Hematol. Infect. Dis.* **2020**, *12*, e2020041. [CrossRef] [PubMed]
2. Brotanek, J.M.; Gosz, J.; Weitzman, M.; Flores, G. Secular Trends in the Prevalence of Iron Deficiency Among US Toddlers, 1976–2002. *Arch. Pediatr. Adolesc. Med.* **2008**, *162*, 374–381. [CrossRef]
3. Powers, J.M.; McCavit, T.L.; Buchanan, G.R. Management of iron deficiency anemia: A survey of pediatric hematology/oncology specialists. *Pediatr. Blood Cancer* **2015**, *62*, 842–846. [CrossRef] [PubMed]

4. Tolkien, Z.; Stecher, L.; Mander, A.P.; Pereira, D.I.A.; Powell, J.J. Ferrous Sulfate Supplementation Causes Significant Gastrointestinal Side-Effects in Adults: A Systematic Review and Meta-Analysis. *PLoS ONE* **2015**, *10*, e0117383. [CrossRef]

5. Fiorino, G.; Colombel, J.-F.; Katsanos, K.; Mearin, F.; Stein, J.; Andretta, M.; Antonacci, S.; Arenare, L.; Citraro, R.; Dell'orco, S.; et al. Iron deficiency anemia impacts disease progression and healthcare resource consumption in patients with inflammatory bowel disease: A real-world evidence study. *Ther. Adv. Gastroenterol.* **2023**, *16*, 17562848231177153. [CrossRef] [PubMed]

6. Smith, J.M.; Jacobson-Kelly, A.M.; Donegan, A.M.; Boyle, B.; Maltz, R.M.; Michel, H.K.; Dotson, J.L. Diagnosis and Treatment of Iron Deficiency and Anemia in Youth with Inflammatory Bowel Disease. *J. Pediatr. Gastroenterol. Nutr.* **2022**, *76*, 313–318. [CrossRef] [PubMed]

7. Burisch, J.; Vegh, Z.; Katsanos, K.H.; Christodoulou, D.K.; Lazar, D.; Goldis, A.; O'Morain, C.; Fernandez, A.; Pereira, S.; Myers, S.; et al. Occurrence of Anaemia in the First Year of Inflammatory Bowel Disease in a European Population-based Inception Cohort—An ECCO-EpiCom Study. *J. Crohn's Colitis* **2017**, *11*, 1213–1222. [CrossRef]

8. Stein, J.; Bager, P.; Befrits, R.; Gasche, C.; Gudehus, M.; Lerebours, E.; Magro, F.; Mearin, F.; Mitchell, D.; Oldenburg, B.; et al. Anaemia management in patients with inflammatory bowel disease: Routine practice across nine European countries. *Eur. J. Gastroenterol. Hepatol.* **2013**, *25*, 1456–1463. [CrossRef] [PubMed]

9. Gasche, C.; Berstad, A.; Befrits, R.; Beglinger, C.; Dignass, A.; Erichsen, K.; Gomollon, F.; Hjortswang, H.; Koutroubakis, I.; Kulnigg, S.; et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm. Bowel Dis.* **2007**, *13*, 1545–1553. [CrossRef]

10. Van Assche, G.; Dignass, A.; Bokemeyer, B.; Danese, S.; Gionchetti, P.; Moser, G.; Beaugerie, L.; Gomollón, F.; Häuser, W.; Herrlinger, K.; et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 3: Special situations. *J. Crohn's Colitis* **2013**, *7*, 1–33. [CrossRef] [PubMed]

11. Domellöf, M.; Szitanyi, P.; Simchowitz, V.; Franz, A.; Mimouni, F. ESPGHAN/ESPEN/ESPR/CSPEN Working Group on Pediatric Parenteral Nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. *Clin. Nutr.* **2018**, *37*, 2354–2359. [CrossRef]

12. Marchasin, S.; Wallerstein, R.O. The Treatment of Iron-Deficiency Anemia with Intravenous Iron Dextran. *Blood* **1964**, *23*, 354–358. [CrossRef]

13. Hamstra, R.D.; Block, M.H.; Schocket, A.L. Intravenous Iron Dextran in Clinical Medicine. *JAMA* **1980**, *243*, 1726–1731. [CrossRef]

14. Chertow, G.M.; Mason, P.D.; Vaage-Nilsen, O.; Ahlmén, J. Update on adverse drug events associated with parenteral iron. *Nephrol. Dial. Transplant.* **2006**, *21*, 378–382. [CrossRef]

15. Rodgers, G.M.; Auerbach, M.; Cella, D.; Chertow, G.M.; Coyne, D.W.; Glaspy, J.A.; Henry, D.H. High-Molecular Weight Iron Dextran: A Wolf in Sheep's Clothing? *J. Am. Soc. Nephrol.* **2008**, *19*, 833–834. [CrossRef]

16. Geisser, P.; Burckhardt, S. The Pharmacokinetics and Pharmacodynamics of Iron Preparations. *Pharmaceutics* **2011**, *3*, 12–33. [CrossRef]

17. Halpin, T.C.; Bertino, J.S.; Rothstein, F.C.; Kurczynski, E.M.; Reed, M.D. Iron-Deficiency Anemia in Childhood Inflammatory Bowel Disease: Treatment with Intravenous Iron-Dextran. *J. Parenter. Enter. Nutr.* **1982**, *6*, 9–11. [CrossRef]

18. Mamula, P.; Piccoli, D.A.; Peck, S.N.; Markowitz, J.E.; Baldassano, R.N. Total Dose Intravenous Infusion of Iron Dextran for Iron-Deficiency Anemia in Children with Inflammatory Bowel Disease. *J. Pediatr. Gastroenterol. Nutr.* **2002**, *34*, 286–290. [CrossRef]

19. Auerbach, M.; Macdougall, I.C. Safety of intravenous iron formulations: Facts and folklore. *Blood Transfus.* **2014**, *12*, 296–300. [CrossRef]

20. Mantadakis, E. Advances in Pediatric Intravenous Iron Therapy. *Pediatr. Blood Cancer* **2015**, *63*, 11–16. [CrossRef]

21. Caimmi, S.; Crisafulli, G.; Franceschini, F.; Liotti, L.; Bianchi, A.; Bottau, P.; Mori, F.; Triggiano, P.; Paglialunga, C.; Saretta, F.; et al. Hypersensitivity to Intravenous Iron Preparations. *Children* **2022**, *9*, 1473. [CrossRef]

22. Ganzoni, A.M. Kinetics and regulation of erythrocyte production. Experimental studies on normal and anemic rats. *Exp. Med. Pathol. Klin.* **1970**, *31*, 1–94.

23. Ganzoni, A.M. New aspects of iron deficiency. *Schweiz. Med. Wochenschr.* **1970**, *100*, 691–697.

24. Avni, T.; Bieber, A.; Grossman, A.; Green, H.; Leibovici, L.; Gafter-Gvili, A. The Safety of Intravenous Iron Preparations. *Mayo Clin. Proc.* **2015**, *90*, 12–23. [CrossRef]

25. Bullen, J.J.; Ward, C.G.; Rogers, H.J. The critical role of iron in some clinical infections. *Eur. J. Clin. Microbiol. Infect. Dis.* **1991**, *10*, 613–617. [CrossRef]

26. Michels, K.R.; Lambrecht, N.J.; Carson, W.F.; A Schaller, M.; Lukacs, N.W.; Bermick, J.R. The Role of Iron in the Susceptibility of Neonatal Mice to *Escherichia coli* K1 Sepsis. *J. Infect. Dis.* **2019**, *220*, 1219–1229. [CrossRef]

27. Bircher, A.J.; Auerbach, M. Hypersensitivity from Intravenous Iron Products. *Immunol. Allergy Clin. N. Am.* **2014**, *34*, 707–723. [CrossRef]

28. Rampton, D.; Folkersen, J.; Fishbane, S.; Hedenus, M.; Howaldt, S.; Locatelli, F.; Patni, S.; Szebeni, J.; Weiss, G. Hypersensitivity reactions to intravenous iron: Guidance for risk minimization and management. *Haematologica* **2014**, *99*, 1671–1676. [CrossRef]

29. Szebeni, J.; Fishbane, S.; Hedenus, M.; Howaldt, S.; Locatelli, F.; Patni, S.; Rampton, D.; Weiss, G.; Folkersen, J. Hypersensitivity to intravenous iron: Classification, terminology, mechanisms and management. *Br. J. Pharmacol.* **2015**, *172*, 5025–5036. [CrossRef]

30. Wang, C.; Graham, D.J.; Kane, R.C.; Xie, D.; Wernecke, M.; Levenson, M.; MaCurdy, T.E.; Houstoun, M.; Ryan, Q.; Wong, S.; et al. Comparative Risk of Anaphylactic Reactions Associated with Intravenous Iron Products. *JAMA* **2015**, *314*, 2062–2068. [CrossRef]

31. Mulder, M.B.; van Den Hoek, H.L.; Birnie, E.; van Tilburg, A.J.; Westerman, E.M. Comparison of hypersensitivity reactions of intravenous iron: Iron isomaltoside-1000 (Monofer®) versus ferric carboxy-maltose (Ferinject®). A single center, cohort study. *Br. J. Clin. Pharmacol.* **2018**, *85*, 385–392. [CrossRef]

32. Pollock, R.F.; Biggar, P. Indirect methods of comparison of the safety of ferric derisomaltose, iron sucrose and ferric carboxymaltose in the treatment of iron deficiency anemia. *Expert Rev. Hematol.* **2020**, *13*, 187–195. [CrossRef] [PubMed]

33. Durup, D.; de Muckadell, P.S.; Strom, C.C. Evaluation of the reported rates of hypersensitivity reactions associated with iron dextran and ferric carboxymaltose based on global data from VigiBase™ and IQVIA™ MIDAS® over a ten-year period from 2008 to 2017. *Expert Rev. Hematol.* **2020**, *13*, 557–564. [CrossRef] [PubMed]

34. Weber, J.C.P. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. *Adv. Inflam. Res.* **1984**, *6*, 1.

35. Nathell, L.; Gohlke, A.; Wohlfeil, S. Reported Severe Hypersensitivity Reactions after Intravenous Iron Administration in the European Economic Area (EEA) Before and After Implementation of Risk Minimization Measures. *Drug Saf.* **2019**, *43*, 35–43. [CrossRef] [PubMed]

36. Plummer, E.S.; Crary, S.E.; McCavit, T.L.; Buchanan, G.R. Intravenous low molecular weight iron dextran in children with iron deficiency anemia unresponsive to oral iron. *Pediatr. Blood Cancer* **2013**, *60*, 1747–1752. [CrossRef] [PubMed]

37. Boucher, A.A.; Pfeiffer, A.; Bedel, A.; Young, J.; McGann, P.T. Utilization trends and safety of intravenous iron replacement in pediatric specialty care: A large retrospective cohort study. *Pediatr. Blood Cancer* **2018**, *65*, e26995. [CrossRef] [PubMed]

38. Surico, G.; Muggeo, P.; Muggeo, V.; Lucarelli, A.; Martucci, T.; Daniele, R.; Rigillo, N. Parenteral iron supplementation for the treatment of iron deficiency anemia in children. *Ann. Hematol.* **2002**, *81*, 154–157. [CrossRef]

39. Michaud, L.; Guimber, D.; Mention, K.; Neuville, S.; Froger, H.; Gottrand, F.; Turck, D. Tolerance and efficacy of intravenous iron saccharate for iron deficiency anemia in children and adolescents receiving long-term parenteral nutrition. *Clin. Nutr.* **2002**, *21*, 403–407. [CrossRef]

40. Pinsk, V.; Levy, J.; Moser, A.; Yerushalmi, B.; Kapelushnik, J. Efficacy and safety of intravenous iron sucrose therapy in a group of children with iron deficiency anemia. *Isr. Med. Assoc. J.* **2008**, *10*, 335–338.

41. Crary, S.E.; Hall, K.; Buchanan, G.R. Intravenous iron sucrose for children with iron deficiency failing to respond to oral iron therapy. *Pediatr. Blood Cancer* **2010**, *56*, 615–619. [CrossRef] [PubMed]

42. Mantadakis, E.; Tsouvala, E.; Xanthopoulou, V.; Chatzimichael, A. Intravenous iron sucrose for children with iron deficiency anemia: A single institution study. *World J. Pediatr.* **2015**, *12*, 109–113. [CrossRef] [PubMed]

43. Kaneva, K.; Chow, E.; Rosenfield, C.G.; Kelly, M.J. Intravenous Iron Sucrose for Children with Iron Deficiency Anemia. *J. Pediatr. Hematol.* **2017**, *39*, e259–e262. [CrossRef]

44. Sharma, R.; Stanek, J.R.; Koch, T.L.; Grooms, L.; O'Brien, S.H. Intravenous iron therapy in non-anemic iron-deficient menstruating adolescent females with fatigue. *Am. J. Hematol.* **2016**, *91*, 973–977. [CrossRef] [PubMed]

45. Houston, B.L.; Hurrie, D.; Graham, J.; Perija, B.; Rimmer, E.; Rabbani, R.; Bernstein, C.N.; Turgeon, A.F.; A Fergusson, D.; Houston, D.S.; et al. Efficacy of iron supplementation on fatigue and physical capacity in non-anaemic iron-deficient adults: A systematic review of randomised controlled trials. *BMJ Open* **2018**, *8*, e019240. [CrossRef] [PubMed]

46. Sabe, R.; Vatsayan, A.; Mahran, A.; Khalili, A.S.; Ahuja, S.; Sferra, T.J. Safety and Efficacy of Intravenous Iron Sucrose for Iron-Deficiency Anemia in Children and Adolescents with Inflammatory Bowel Disease. *Glob. Pediatr. Health* **2019**, *6*, 2333794X19870981. [CrossRef] [PubMed]

47. Grim, K.; Lee, B.; Sung, A.Y.; Kotagal, S. Treatment of childhood-onset restless legs syndrome and periodic limb movement disorder using intravenous iron sucrose. *Sleep Med.* **2013**, *14*, 1100–1104. [CrossRef]

48. Keating, G.M. Ferric Carboxymaltose: A Review of Its Use in Iron Deficiency. *Drugs* **2014**, *75*, 101–127. [CrossRef]

49. Evstatiev, R.; Alexeeva, O.; Bokemeyer, B.; Chopey, I.; Felder, M.; Gudehus, M.; Iqbal, T.; Khalif, I.; Marteau, P.; Stein, J.; et al. Ferric Carboxymaltose Prevents Recurrence of Anemia in Patients with Inflammatory Bowel Disease. *Clin. Gastroenterol. Hepatol.* **2013**, *11*, 269–277. [CrossRef]

50. Evstatiev, R.; Marteau, P.; Iqbal, T.; Khalif, I.L.; Stein, J.; Bokemeyer, B.; Chopey, I.V.; Gutzwiller, F.S.; Riopel, L.; Gasche, C. FERGIcor, a Randomized Controlled Trial on Ferric Carboxymaltose for Iron Deficiency Anemia in Inflammatory Bowel Disease. *Gastroenterology* **2011**, *141*, 846–853.e2. [CrossRef]

51. Powers, J.M.; Shamoun, M.; McCavit, T.L.; Adix, L.; Buchanan, G.R. Intravenous Ferric Carboxymaltose in Children with Iron Deficiency Anemia Who Respond Poorly to Oral Iron. *J. Pediatr.* **2016**, *180*, 212–216. [CrossRef]

52. Mantadakis, E.; Roganovic, J. Safety and efficacy of ferric carboxymaltose in children and adolescents with iron deficiency anemia. *J. Pediatr.* **2017**, *184*, 241. [CrossRef] [PubMed]

53. Bevers, N.; Van de Vijver, E.; Aliu, A.; Ardabili, A.R.; Rosias, P.; Stapelbroek, J.; Maartens, I.A.B.; van de Feen, C.; Escher, H.; Oudshoorn, A.; et al. Ferric Carboxymaltose Versus Ferrous Fumarate in Anemic Children with Inflammatory Bowel Disease: The POPEYE Randomized Controlled Clinical Trial. *J. Pediatr.* **2022**, *256*, 113–119.e4. [CrossRef]

54. Kaenkumchorn, T.K.; Rosete, B.E.; Carlin, K.; Fukasawa, S.; Horslen, S.P.; Wendel, D. Analysis of transition from intravenous iron sucrose to ferric carboxymaltose infusions in pediatric patients with intestinal failure. *J. Parenter. Enter. Nutr.* **2022**, *46*, 1578–1584. [CrossRef] [PubMed]

55. Korczowski, B.; Farrell, C.; Falone, M.; Blackman, N.; Rodgers, T. Safety, pharmacokinetics, and pharmacodynamics of intravenous ferric carboxymaltose in children with iron deficiency anemia. *Pediatr. Res.* **2023**, *94*, 1547–1554. [CrossRef]

56. Laass, M.W.; Straub, S.; Chainey, S.; Virgin, G.; Cushway, T. Effectiveness and safety of ferric carboxymaltose treatment in children and adolescents with inflammatory bowel disease and other gastrointestinal diseases. *BMC Gastroenterol.* **2014**, *14*, 184. [CrossRef]

57. Gordon, M.; Sinopoulou, V.; Iheozor-Ejiofor, Z.; Iqbal, T.; Allen, P.; Hoque, S.; Engineer, J.; Akobeng, A.K. Interventions for treating iron deficiency anaemia in inflammatory bowel disease. *Cochrane Database Syst. Rev.* **2021**, *2021*, CD013529. [CrossRef]

58. Aksan, A.; Işık, H.; Radeke, H.H.; Dignass, A.; Stein, J. Systematic review with network meta-analysis: Comparative efficacy and tolerability of different intravenous iron formulations for the treatment of iron deficiency anaemia in patients with inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **2017**, *45*, 1303–1318. [CrossRef]

59. Panagopoulou, P.; Alexiadou, S.; Ntoumpara, M.; Papazoglou, A.; Makis, A.; Tragiannidis, A.; Fotoulaki, M.; Mantadakis, E. Safety of Ferric Carboxymaltose in Children: Report of a Case Series from Greece and Review of the Literature. *Pediatr. Drugs* **2022**, *24*, 137–146. [CrossRef]

60. Schaefer, B.; Tobiasch, M.; Wagner, S.; Glodny, B.; Tilg, H.; Wolf, M.; Zoller, H. Hypophosphatemia after intravenous iron therapy: Comprehensive review of clinical findings and recommendations for management. *Bone* **2022**, *154*, 116202. [CrossRef]

61. Edmonston, D.; Wolf, M. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. *Nat. Rev. Nephrol.* **2020**, *16*, 7–19. [CrossRef] [PubMed]

62. Wolf, M.; Koch, T.A.; Bregman, D.B. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J. Bone Miner. Res.* **2013**, *28*, 1793–1803. [CrossRef] [PubMed]

63. Wolf, M.; Rubin, J.; Achebe, M.; Econs, M.J.; Peacock, M.; Imel, E.A.; Thomsen, L.L.; Carpenter, T.O.; Weber, T.; Brandenburg, V.; et al. Effects of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Iron-Deficiency Anemia: Two Randomized Clinical Trials. *JAMA* **2020**, *323*, 432. [CrossRef] [PubMed]

64. Schaefer, B.; Tobiasch, M.; Viveiros, A.; Tilg, H.; Kennedy, N.A.; Wolf, M.; Zoller, H. Hypophosphataemia after treatment of iron deficiency with intravenous ferric carboxymaltose or iron isomaltoside—A systematic review and meta-analysis. *Br. J. Clin. Pharmacol.* **2020**, *87*, 2256–2273. [CrossRef] [PubMed]

65. Posod, A.; Schaefer, B.; Mueller, T.; Zoller, H.; Kiechl-Kohlendorfer, U. Hypophosphatemia in children treated with ferric carboxymaltose. *Acta Paediatr.* **2020**, *109*, 1491–1492. [CrossRef] [PubMed]

66. Cococcioni, L.; Pensabene, L.; El-Khouly, S.; Chadokufa, S.; McCartney, S.; Saliakellis, E.; Kiparissi, F.; Borrelli, O. Ferric carboxy-maltose treatment for iron deficiency anemia in children with inflammatory bowel disease: Efficacy and risk of hypophosphatemia. *Dig. Liver Dis.* **2021**, *53*, 830–834. [CrossRef]

67. Kirk, S.E.; Scheurer, M.E.; Bernhardt, M.B.; Mahoney, D.H.; Powers, J.M. Phosphorus levels in children treated with intravenous ferric carboxymaltose. *Am. J. Hematol.* **2021**, *96*, E215–E218. [CrossRef]

68. Russo, G.; Guardabasso, V.; Romano, F.; Corti, P.; Samperi, P.; Condorelli, A.; Sainati, L.; Maruzzi, M.; Facchini, E.; Fasoli, S.; et al. Monitoring oral iron therapy in children with iron deficiency anemia: An observational, prospective, multicenter study of AIEOP patients (Associazione Italiana Emato-Oncologia Pediatrica). *Ann. Hematol.* **2020**, *99*, 413–420. [CrossRef]

69. Mantadakis, E. Intravenous iron: Safe and underutilized in children. *Pediatr. Blood Cancer* **2018**, *65*, e27016. [CrossRef]