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CRITICAL REVIEW

Expert consensus guidelines: Intravenous iron uses, formulations, administration, and management of reactions

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Abstract

Intravenous iron has become an essential component for the treatment of iron deficiency and iron deficiency anemia. Individuals administering Intravenous iron should have knowledge in intravenous iron administration, including a pre-infusion assessment to evaluate infusion reaction risks, pre- and post-infusion monitoring, identification of and management of infusion reactions, accurate documentation of these reactions, laboratory monitoring and recognition and management of treatment-emergent hypophosphatemia. This comprehensive consensus provides step-by-step guidance and tools for practitioners to promote safe delivery of intravenous iron, recognition, and management of infusion reactions and treatment-emergent hypophosphatemia.

1 | INTRODUCTION

Intravenous (IV) iron has become an essential component for the treatment of iron deficiency (ID) and iron deficiency anemia (IDA). Earlier formulations, no longer in use, were associated with unacceptable toxicity. Newer iron formulations allow for a total dose infusion (TDI) in 15 to 60 min, obviating multiple unnecessary visits for the same clinical benefit without added toxicity. The elemental iron in these formulations is bound more tightly to the complex carbohydrate core, resulting in fewer infusion reactions.[1] The most common infusion reaction is complement activated related pseudo-allergy (CARPA), also known as a Fishbane reaction, which is physiologically different from an anaphylactic reaction.[2] Anaphylaxis due to IV iron is exceedingly rare, occurring with <1:200000 administrations.[3] Herein, we provide a comprehensive consensus guideline for the administration of IV iron, recognition and management of infusion reactions and treatment-emergent hypophosphatemia. This consensus document will dispel the folklore of danger that has been associated with IV iron use and serve as a guide to the hematologist and others who administer IV iron.

A modified Delphi strategy was used to develop recommendations for IV iron administration, identification, and classification of infusion reactions, pre- and post-infusion monitoring, and recognition and management of treatment-emergent hypophosphatemia. An expert group consisting of five clinicians (2 physicians, 2 nurse practitioners and a pharmacist), all specializing in the care of persons with ID and IDA, was selected to form the consensus. This expert group is responsible for the administration and supervision of thousands of

doses of IV iron annually. As a result, expert clinical experience will be provided along with available data, and a careful description of current labeling. In those circumstances in which consensus diverges with FDA approved methods of administration, peer reviewed evidence for the recommendation is provided.

2 | METHODS

The Delphi method is a structured process used to produce a well-grounded consensus by a group of experts using an iterative process of survey rounds with controlled feedback.[4] After an initial video-conference meeting to discuss and confirm the outline of this guidance paper, the group conducted a comprehensive literature search to develop a draft for each section. The primary author compiled the drafted sections noting the aspects where there was a lack of evidence or divergence from FDA labeling, necessitating expert consensus. Anonymity of each expert's responses in this methodology removed the bias that could occur with face-to-face group meetings by hearing the opinions of the others in the group. The primary author (moderator) provided each expert with the items requiring consensus. After each round, the moderator collected the group's responses, analyzed them, and presented them back to the group. Aspects that reached consens's were dropped from the next round. Consensus was defined as two-thirds consensus (Table 1).

3 | THE INTRAVENOUS IRON FORMULATIONS

There are seven IV iron formulations available for use in the United States. Most of these agents are available in Europe and Asia, with some exceptions. Two iron salts, ferric gluconate, and iron sucrose have been reported to be safe and effective across a host of conditions associated with ID.[5,6] The carbohydrate carriers, gluconate and sucrose, bind elemental iron less tightly than the other five formulations discussed below, releasing labile free iron at much higher levels resulting in unacceptable infusion reactions at doses above 200–250 mg.[1] In this setting, four to seven visits are required for complete replenishment of iron. In that every head-to-head comparison of the salts to the four formulations which enable a TDI reported no difference in efficacy or safety, for ambulatory patients receiving IV iron their use is suboptimal. On the other hand, a TDI obviates unnecessary multiple visits, decreases the likelihood of an extravasation which may stain the skin and reduces the likelihood of infusion reactions. Subsequently, the guidance will limit the discussion to formulations capable of being administered in a replacement dose of 1000 mg (or more) in a single 15 to 60-min visit (Table 2). These formulations are (in order of approval in the United States) low molecular weight iron dextran (LMWID), ferumoxytol, ferric carboxymaltose (FCM), ferric derisomaltose (FDI) and ferumoxytol generic. The indications, monitoring, adverse events profile, and its management, approved and recommended methods of infusion will be discussed.

TABLE 1 Consensus recommendations.

Formulations administered as a single TDI are recommended over formulations requiring multiple dose infusions
Optimal Formulations for TDI: ferumoxytol, LMWID, FDI Suboptimal Formulations for TDI: ferumoxytol generic, FCM, iron sucrose, iron gluconate
Administer Ferumoxytol as a TDI of 1020 mg in 30 min
Pregnancy: Avoid IV iron prior to 13 weeks gestation. Recommend against fetal monitoring during and following IV iron administration
Monitoring for 30 min post-IV iron administration is not indicated
Premedication should be reserved for those persons at high risk of HSRs
Allow 30 min between administration of IV iron & other medications[a] at high risk for HSRs.
Ferritin goal of 50 ng/mL regardless of sex at birth
Manage infusion reactions as outlined in Figure 2
Rechallenge with the same IV iron formulation may be attempted following an infusion reaction
Phosphorus monitoring following IV iron administration should be guided by clinical symptoms for all formulations except FCM[b]
Management of treatment-emergent hypophosphatemia is directed at preventing secondary hypoparathyroidism

Abbreviations: FCM, ferric carboxymaltose; FDI, ferric derisomaltose; HSRs, hypersensitivity reactions; LMWID, low molecular weight iron dextran.
[a]Chemotherapeutic agents or monoclonal antibodies.
[b]See package insert for phosphorus monitoring post-treatment with FCM.

3.1 | Low molecular weight iron dextran (LMWID)

LMWID was the first of the four formulations to be approved in the US. This is not to be confused with older formulations of high molecular weight iron dextrans which are no longer available. These older formulations were associated with an alarmingly high incidence of adverse events, up to 28% in one study.[7]

LMWID carries a black box warning of anaphylaxis in the United States but not in Europe, despite no support for this iteration. While the current label for LMWID is a 100 mg bolus over 2 min, this is an undesirable method of administration, requires 10 visits to accomplish what can be done in one, is much more expensive, and far less convenient. Multiple studies have reported the safety, efficacy, and convenience of a single infusion of 1000 mg in 1 h.[8–11] Equal efficacy and safety has been shown with LMWID when compared to iron sucrose and FCM.[12]

LMWID should be administered as a 1000 mg infusion in 250 mL of normal saline. To monitor for infusion reactions as per FDA label, there are two options; initiate the infusion slowly for approximately 5 min or administer a 25 mg test dose by using a syringe filled with the diluted solution and injecting it slowly over the same amount of time. If no reaction is observed, the remaining solution should be infused over the balance of 1 h. If a minor infusion reaction is observed, it should be treated in the same manner as a minor infusion with any of the other formulations, discussed further below.

TABLE 2 Intravenous iron formulations.

Trade Name	INFeD-US Cosmofer-Europe	Feraheme	Injectafer-US Ferinject-Europe	Monoferric Monofer-Europe
Manufacturer	AbbVie	Covis	Daiichi Sankyo	Pharmacosmos
Carbohydrate	Low molecular weight iron dextran	Ferumoxytol	Carboxymaltose	Derisomaltose
Total dose infusion (TDI)[a]	Yes	No	Yes- Europe/No- US	Yes
Test dose required	Yes	No	No	No
Approved dose	100 mg per dose	510 mg	1000 mg Europe[b] 750 mg US[b]	1000 mg 20 mg/kg if <50 kg
Optimal dose	1000 mg	1020 mg	1000 mg Europe/750 mg US	1000 mg
Infusion time	60 min	30 min	15 min	20 min

Note: Intravenous iron products allowing total dose infusion (TDI).
[a]See package insert of each formulation for full prescribing information.
[b]Patients <50 kg, 15 mg/kg in two divided doses 1 week apart.

3.2 | Ferumoxytol

Ferumoxytol is a superparamagnetic iron-oxide linked to polyglucose-sorbitol carboxymethylether that was originally designed as an MRI contrast agent due to its molecular properties.[13] As a result, if MRI is planned within 8 weeks of administration, radiologists must be notified of its presence so to not confound interpretation.[14] Following administration, significant improvements in hemoglobin concentrations were observed in iron deficient individuals. This led to its approval for treatment of ID in patients with chronic kidney disease (CKD). Unfortunately, the first approved method of administration was to inject 510 mg (vial concentration is 510 mg in 17 mL) in 17 s, or 1 mL per second, in two divided doses 1 week apart. Although the stable superparamagnetic iron oxide coated with polyglucose sorbitol carboxymethylether is very stable, releasing low amounts of labile free iron, the extremely rapid injection led to a high incidence of infusion reactions, many of which were misinterpreted as anaphylaxis.[15] Subsequently, the label was changed to infuse 510 mg in not <15 min in two divided doses 1 week apart. Using this method of administration, the incidence of serious adverse events is vanishingly rare with minor infusion reactions occurring at the same 1%–3% incidence as with the other formulations.[16] Equal safety and efficacy of ferumoxytol has been shown when compared with iron sucrose[17,18] and FCM.[19]

While this latter method of administration remains as the current label, several studies have reported the safety and efficacy of administration of 1020 mg in a single 30 min infusion without a single serious adverse event.[20–22] Insurance permitting, ferumoxytol can be administered as 1020 mg (two vials) in 100 mL of normal saline and infused over 30 min. As with all formulations, the infusion should start slowly and be observed for several minutes. If no reaction occurs, the remaining solution should be infused over the balance of 30 min.

3.3 | Ferumoxytol generic

There are no published safety or efficacy data on this formulation of IV iron; therefore, what follows in this section is expert experience. In 2022, FDA approved ferumoxytol generic based on molecular identity to ferumoxytol. While such an iteration may work for smaller molecules, the very high molecular weight of the newer iron formulations makes it unlikely that a generic copy is truly identical. Funk et al., reported the differences in surface chemistry between the iron-carbohydrate complexes that resulted in significant differences between in vivo pharmacokinetic and pharmacodynamic profiles as well as adverse event profiles, demonstrating that the entire iron-carbohydrate complex furnishes the pharmacologic action for these complex formulations.[23] Currently available physicochemical characterization methods have limitations in biorelevant behavior resulting in challenges in defining critical quality attributes for surface characteristics for this class of complex medications. This was the case when HMWID was approved in 1996, as a less expensive alternative to LMWID, leading to an increase in serious adverse events. Such appears to be the case with ferumoxytol generic. In their filing with FDA, Sandoz submitted the results of 60 patients who received the generic formulation. The incidence of infusion reactions was double that of the brand. There was a death with the generic, corroborated by checking national drug codes. Without published data on this formulation, practitioners should exercise caution with its use. Pharmacists have the right to substitute the generic if the brand is ordered unless the brand is mandated. At present the recommendations for infusing generic ferumoxytol are the same as for the brand.

3.4 | Ferric carboxymaltose (FCM)

FCM is a macromolecular ferric hydroxide carbohydrate complex which facilitates slow release of elemental iron after injection, allowing a large dose of 1000 mg to be administered in 15 to 30 min.[24] Throughout Europe and Asia, FCM is routinely administered as a 1000 mg single infusion. It has been shown to be safe and efficacious across a host of conditions associated with iron lack, including CKD,[25] pregnancy,[26,27] heavy uterine bleeding,[28] inflammatory bowel disease,[29] and congestive heart failure.[30] FCM was the first IV iron formulation to be associated with fewer cardiovascular events and hospitalizations after administration for ID in patients with congestive heart failure.[31]

In the United States FCM is distributed exclusively as a 750 mg vial with a label to administer two doses 1 week apart, requiring a minimum dose of 1500 mg or the wastage of 500 mg if 1 g is the desired dose. FCM administration has also come to be associated with treatment-emergent hypophosphatemia and should be avoided in patients who require repeat infusions,[32] discussed in detail below. FCM should be diluted in 100 mL of normal saline and infused over 20–30 min, with the same precautions as the other formulations to observe for acute onset of minor infusion reactions.

3.5 | Ferric derisomaltose (FDI)

FDI was the last of the formulations allowing administration as a TDI to be approved in the United States in 2020 but was in use throughout Europe from 2009. It was approved in Canada in 2018. FDI is a short linear structure of linked glucose units forming a unique carbohydrate matrix allowing binding to elemental iron similarly to ferumoxytol and FCM.[33] FDI is the only formulation to have a FDA label for a total dose infusion.

As is the case with the other formulations, FDI has been compared with iron sucrose[6,34,35] and FCM and reported to be equally safe and efficacious.[36,37] FDI is safe and efficacious for the management of CKD,[38] pregnancy,[39] inflammatory bowel disease,[32] and most recently in iron deficient patients with congestive heart failure.[40] In this latter trial, FDI was the first IV iron formulation to report a statistically significant decrement in death from cardiovascular events in patients with congestive heart failure.

FDI is approved for a 1000 mg infusion or doses up to 20 mg/kg not to exceed 1500 mg. It should be diluted in 100 mL of normal saline and infused with the same precautions as the other formulations.

3.5.1 | Frequency of administration

The frequency of administration and duration of benefit is dependent on the underlying etiology of the ID. If the cause has been eliminated a single TDI should suffice. However, if there are ongoing losses (heavy menstrual bleeding, angiodysplasia (hereditary hemorrhagic telangiectasia), inflammatory bowel disease) or a condition in which iron absorption is inhibited (after bariatric surgery, autoimmune gastritis, celiac disease), multiple administrations are necessary. The frequency depends on the degree of blood loss or malabsorption.

4 | LAB MONITORING

Monitoring following iron repletion is dependent on the underlying pathology that increases the risk of ongoing ID and IDA. Treatment in ID and IDA should be to replenish iron stores and treat the underlying pathology. Phosphate monitoring post-IV iron infusion is discussed further in the section on treatment-emergent hypophosphatemia.

Laboratory evaluation following IV iron should include a CBC and iron parameters (ferritin, percent transferrin saturation (TSAT) calculated by dividing the serum iron by the total iron binding capacity (TIBC)) 4 to 8 weeks after the last infusion. Iron parameters should not be evaluated within 4 weeks of a TDI, as the circulating iron interferes with the assay leading to specious results. Hemoglobin concentrations should increase within 1–2 weeks of treatment and should increase by 1 to 2 g/dL within 4–8 weeks of therapy. Traditional tests to diagnose ID and monitor the response to IV iron have limitations but ferritin and TSAT have remained the best performing tests. In the absence of inflammation, the goal ferritin is 50 ng/mL, regardless of sex at birth.[41]

Ferritin synthesis is dependent on cellular iron and even during states of inflammation where absolute ID is present the rise in ferritin is blunted.[41] Situations may arise where the TSAT and ferritin present a discordant depiction of iron status. The serum ferritin may be elevated, because of its acute phase reactivity, while the TSAT is low, indicating ID, either absolute or functional. A TSAT <20% has high sensitivity for diagnosing absolute or functional ID, but a ferritin of <100 ng/mL has a low sensitivity of 35%–48%.[42] Soluble transferrin receptor (sTfR) has been shown to be more sensitive in patients with inflammatory conditions where the ferritin (but not the TSAT) is unreliable for evaluation of ID and IDA.[43] sTfR is elevated in those with ID and not affected by inflammation. A limitation is the sTfR is also elevated with increased erythropoietic activity (response to IV iron, hemolytic anemia, etc.) and ineffective erythropoiesis. It is also limited by lack of routine availability, and long turnaround time.

Reticulocyte Hb content is a direct assessment of the functional availability of iron to the erythropoietic tissue. This can be measured by two methods, the reticulocyte hemoglobin content (CHr) or reticulocyte hemoglobin equivalent (RET-He). These are quick and reliable tests for detecting ID and the need for iron replacement. It has the advantage of being immediately available on certain auto analyzers (Siemens and Sysmex).[44] It is limited by the lack of routine availability and can be abnormal in inflammation and thalassemia.

The frequency with which lab monitoring is required post-IV iron infusion is dependent on the cause of the ID. Those with recurrent blood loss will require more frequent and aggressive laboratory monitoring to diagnose and treat ID even in the absence of anemia since ID in the absence of anemia can lead to clinical complications. Patients with an inappropriate response to IV iron should be evaluated for ongoing blood loss or an alternative diagnosis for ID (true and functional).

4.1 | Pregnancy

Administration of IV iron is generally avoided prior to the 13th week of gestation due to a lack of safety data. There is no difference in the administration of IV iron compared with the non-pregnant person, and all IV iron formulations above have been shown to be safe and effective in pregnancy.[21,45–47] Fetal monitoring during or following IV iron administration is not required and the authors recommend against it.

5 | INFUSION REACTION (NON-IGE-MEDIATED HYPERSENSITIVITY) VS. ALLERGIC REACTION (IGE-MEDIATED HYPERSENSITIVITY)

The vast majority of infusion reactions to IV iron labeled as serious adverse events (SAEs) are not IgE-mediated hypersensitivity reactions (non-allergy), but likely complement activation related pseudo-allergy (CARPA), most often a self-limited reaction to labile free iron (Figure 1).[2] Labile iron is weakly bound iron which has been released from the core of the iron carbohydrate nanoparticle and available to bind transferrin.[1] CARPA is thought to be characterized by a complement mediated reaction to either nanoparticles of free or labile iron that do not bind transferrin quickly enough or to the engineered iron carbohydrate nanoparticle.[48,49] It is most often non-life threatening and can occur at any time without prior sensitization, but is most frequently seen at the beginning of the infusion. It is characterized by flushing, myalgias and/or arthralgias, back pain and/or chest pressure. Symptoms of anaphylaxis are not present (systemic hypotension, wheezing, peri-orbital edema, respiratory stridor, or gastrointestinal pain).[50]

All formulations have the potential to cause infusion reactions from labile free iron. However, the various IV iron formulations differ in their physiochemical properties of size, labile iron content, and release of iron in the serum.[1] Because of this, the likelihood of developing CARPA is thought to be proportional to formulation stability and the speed of the infusion.[51] With much smaller cores, ferric gluconate and iron sucrose release larger amounts of labile free iron after injection. As such, administration at lower doses and more frequent visits to achieve the desired dose is required. CARPA is not specific to IV iron and has been observed with other medications, such as monoclonal antibodies and liposomal medications.[52] These reactions usually resolve without treatment.[53]

Contrary to CARPA, a type I hypersensitivity anaphylactic reaction is a systemic life-threatening reaction that is IgE-mediated. Upon exposure to an allergen, cross linking of IgE to FcεRI occurs, culminating in activation of mast cell and basophil degranulation releasing histamine and various proteases, as well as de novo synthesis of many inflammatory mediators such as leukotrienes, prostaglandins, and cytokines.[54] Clinically this can be characterized by airway compromise, mucosal swelling, circulatory manifestations, and gastrointestinal symptoms. Anaphylaxis is a clinical emergency. It can occur with the administration of any parenteral formulation, including chemotherapy and antibiotics.

6 | INFUSION REACTIONS

All staff involved in the management IV iron therapy must be properly educated on the recognition and management of infusion reactions. The patient should be educated on the infusion process and potential infusion reactions that can occur. Although there is no prospective

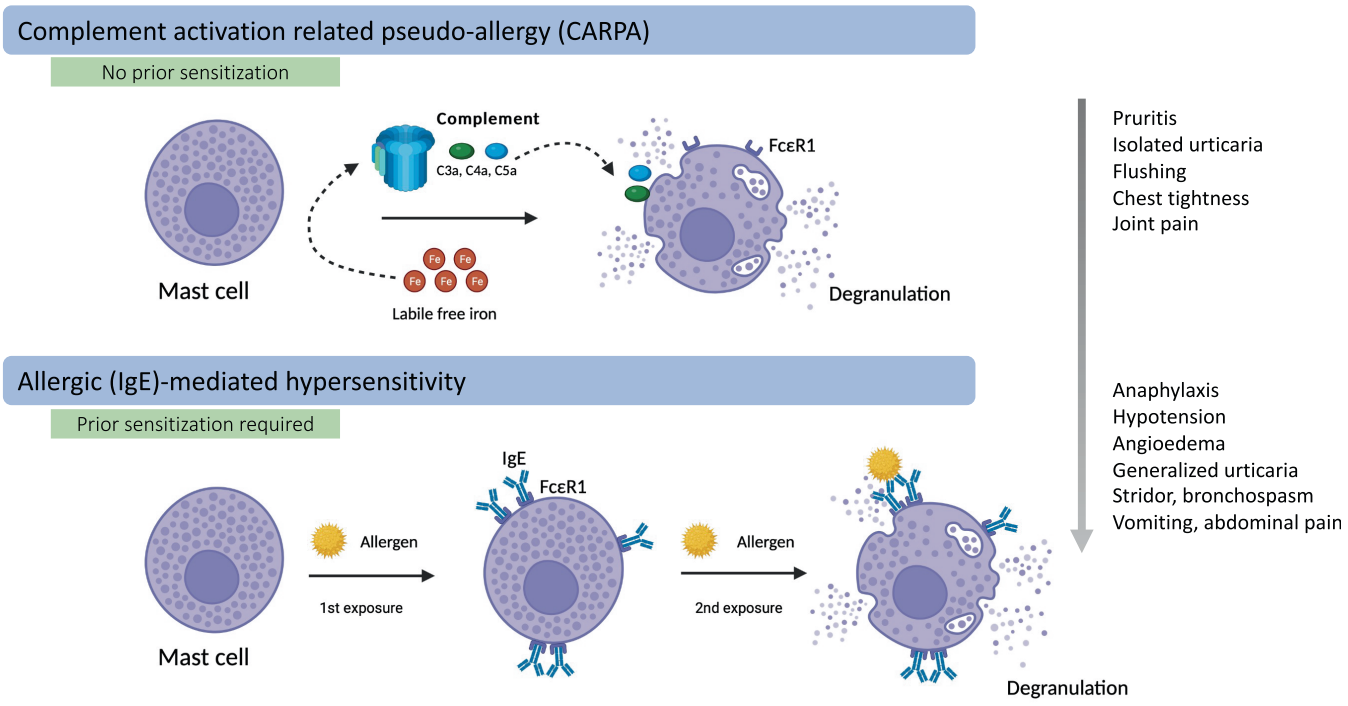

FIGURE 1 CARPA vs. allergic (IgE)-mediated hypersensitivity. Adapted from Alsaleh et al.[49] Top panel: Labile iron activates complement causing mast cell degranulation. No sensitization is required. Bottom panel: Allergic (IgE)-mediated hypersensitivity requires prior sensitization. Upon re-exposure, the allergen cross-links IgE bound to mast cells and causes degranulation. CARPA is usually self-limited while IgE-mediated hypersensitivity can lead to severe symptoms and anaphylaxis. Created with Biorender 2023.

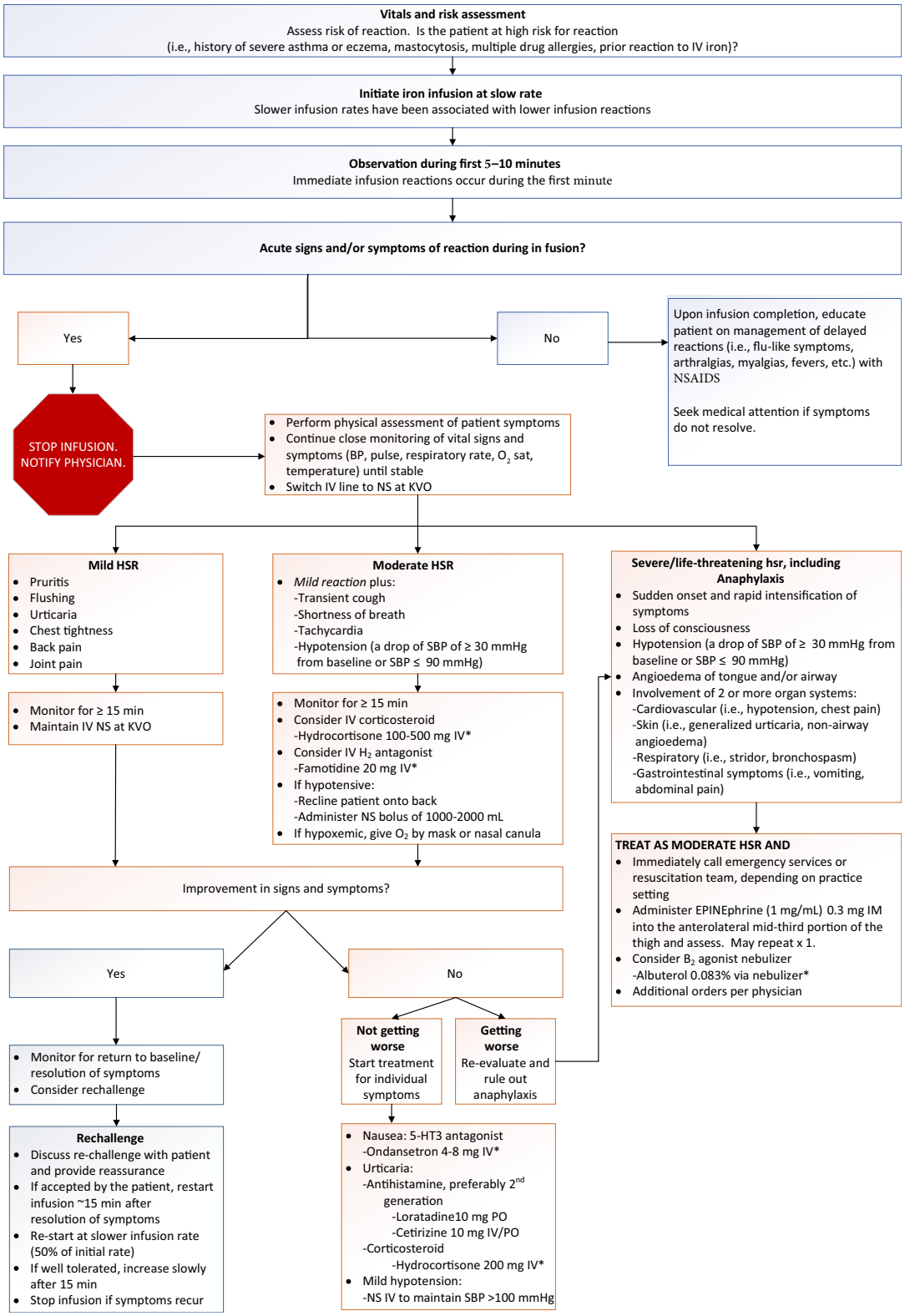

FIGURE 2 Management of infusion reactions, adapted from Achebe et al.[57] IM, intramuscular; IV, intravenous; KVO, describes a slow infusion rate just enough to "keep vein open"; NS, normal saline; PO, by mouth; SBP, systolic blood pressure; * or equivalent therapy.

data to support premedication, it has been shown to mitigate next day arthralgia-myalgia syndrome associated with the total dose infusion LMWID.[55] The use of premedication remains controversial and should be limited to those patients with whom the provider considers to have substantial risk factors for an infusion reaction (multiple drug allergies, prior reaction to an IV iron formulation, asthma).

The recommendation to premedicate is based on low quality data and is left up to the practitioner. However, in patients at risk for an infusion reaction, the infusion should be initiated at a slower rate. First generation antihistamines (H_1 blockers) have been reported to be associated with an increase in adverse reactions and should be avoided.[56]

Irrespective of the severity of the reaction, the infusion should be stopped. A physical assessment and vital signs should be performed. Management of infusion reactions should follow a step-wise approach (Figure 2).[57]

6.1 | Management of mild and moderate infusion reactions

Minor infusion reactions should be managed by stopping the infusion, switching the IV administration to hydration fluid to keep the vein open, and monitoring. For most, these reactions will be self-limiting and resolve spontaneously.[50,56]

After 15 min, continue to monitor until resolution of symptoms. Rechallenge may be considered. If symptoms do not improve or worsen after 15 min, consider administering an IV corticosteroid such as hydrocortisone 200 mg (or equivalent).

Symptom-directed treatment can be administered in the form of a 5-HT3 antagonist (i.e., ondansetron 4 to 8 mg IV) for nausea or a second-generation antihistamine (H_2) (i.e., loratadine 10 mg orally or cetirizine 10 mg IV or oral) for urticaria. Administration of first-generation antihistamines (H_1) (i.e., diphenhydramine) and vasopressors should be avoided, as these medications have the potential to convert minor infusion reactions into hemodynamically significant serious adverse events, including exacerbation of hypotension, tachycardia, diaphoresis, sedation, and shock.[52] Although less so, second-generation antihistamines can also lead to flushing, palpitations and dizziness. Mild hypotension may be managed with IV hydration.

6.2 | Rechallenge following isolated minor and moderate infusion reactions

Patients with mild and moderate infusion reactions with complete resolution of symptoms should be considered for rechallenge. Restart the infusion after the resolution of symptoms at a slower rate; 50% of the initial infusion rate is generally accepted. After 15 min, if the infusion is well tolerated, increase slowly to the desired rate. If symptoms recur, stop the infusion, and manage as previously described, list the symptoms experienced and the management (Table 3).

Although the package insert for all formulations recommend monitoring for 30 min post-infusion, there is no physiological basis to recommend patients be observed for 30 min after an infusion of iron is complete, since IV iron is not associated with a severe delayed reaction.[50] Prior to discharge, patients should be informed of possible delayed infusion reactions, which can occur several hours to days after the infusion. The most common symptoms include flu-like symptoms, arthralgias, myalgias, and fever which may last up to 24 h and are easily managed with non-steroidal anti-inflammatories (NSAIDS). Symptoms lasting more than a few days need to be evaluated by a provider and may be indicative of other pathologies, such as hypophosphatemia when treated with certain IV iron formulations. If subsequent IV iron therapy is required, consider the need for appropriate premedication or an alternative formulation.[56]

TABLE 3 Reporting recommendations following an infusion reaction.

Severity of reaction (mild, moderate, severe)
Timing of symptoms onset and course of progression
Interventions, timing of patient response
Previous iron formulations given, dates, dosage, infusion rate

6.3 | Management of severe or life-threatening infusion reactions

Although extremely rare, severe life-threatening reactions can occur with any iron formulation and constitutes a true medical emergency. Anaphylaxis from IV iron should be managed the same as anaphylaxis from any cause.

7 | TREATMENT-EMERGENT HYPOPHOSPHATEMIA

Treatment-emergent hypophosphatemia is now widely recognized following administration of certain IV iron formulations and occurs within the first 2 weeks after administration.[58] Phosphate is essential for metabolism, bone mineralization, cellular structure, and enzymatic function. Hypophosphatemia is defined by severity as mild (phosphate level < LLN – 2.5 mg/dL), moderate (<2.5 - 2 mg/dL), severe (<2 mg/dL – 1.0 mg/dL), and potentially life threatening (< 1 mg/dL).[58] Symptoms are commonly observed with moderate hypophosphatemia and include fatigue, proximal muscle weakness and bone pain, symptoms which can mimic IDA. Asthenia, myopathy, and respiratory failure have also been reported.[58] Clinical trials,[19,36,59] meta-analyses,[60,61] and systematic reviews[62] have associated the severity and duration of hypophosphatemia to be highest following administration of FCM with the overall incidence ranging between 47% and 75% and <10% treated with LMWID, ferumoxytol and FDI.[63] The only trial to evaluate hypophosphatemia (<2 mg/dL) as a primary outcome is the PHOSPHARE-IBD, which reported an incidence of hypophosphatemia in FCM-treated patients to be 51% at any time from baseline to Day 35.[32] FCM has also been associated with severe and prolonged hypophosphatemia, up to 6 months following administration but the true duration remains unknown.[60]

It is likely the specific physicochemical properties of FCM which triggers the sharp increase in the phosphoturic hormone, iFGF23, leading to hyperphosphaturic hypophosphatemia. This culminates in

low 1,25 (OH)2 vitamin D, hypocalcemia and secondary hyperparathyroidism and has been associated with osteomalacia, fracture, and other bone deformities (Figure 3).[58,64] The degree of phosphorus excretion correlates with a higher glomerular filtration rate (GFR), the magnitude of the increase in iFGF23 and repeat dosing.[65] Patients with impaired kidney function have a lower risk of developing hypophosphatemia due to reduced GFR which limits the filtered amount of phosphate, therefore, limiting the amount excreted in the urine.[65]

It is prudent to identify patients at risk for treatment-emergent hypophosphatemia since it can be prolonged and there is no standard management. The group of persons at risk is broad but those at highest are patients with recurrent blood loss and malabsorptive causes where repeat infusions are required (Table 4).[65] For these patients, FCM can be dangerous and should be avoided, as repeat infusions may lead to osteomalacia and fractures. An alternative formulation to FCM should be considered, where available.[63]

There is no standard of care for managing treatment-emergent hypophosphatemia. It is refractory to oral and IV phosphate supplementation.[66] Vitamin D supplementation before FCM infusion does not reduce hypophosphatemia risk.[65] For mild hypophosphatemia without symptoms, observation is recommended.[67] Treatment should be directed at mitigating secondary hyperparathyroidism, such as with vitamin D supplementation. Phosphate repletion should be avoided as it raises parathyroid hormone and worsens the phosphaturia, ultimately worsening hypophosphatemia.[65] The most important management of hypophosphatemia is cessation of FCM. Due to ongoing safety concerns of FCM, it remains a suboptimal formulation for TDI.

The symptoms of acute hypophosphatemia mirror those of ID and IDA. Patients treated with FCM should be informed to seek medical care if they experience worsening fatigue with myalgias or bone pain following infusion. FDA label for FCM mandates monitoring serum phosphate levels in patients at risk for chronic low serum phosphate, checking phosphate levels in those who are at risk for low serum phosphate who require a repeat course of treatment, and in any patient who receives a second course of treatment within 3 months.[68] Since mild and moderate hypophosphatemia can be asymptomatic and self-limiting in the majority of patients treated with FDI, universal monitoring of phosphorous is not recommended. Consideration for monitoring of phosphorous levels post-FDI is dependent on clinical symptoms of hypophosphatemia. Any patient reporting bone pain should undergo imaging. Protracted hypophosphatemia with FDI has not been reported.

TABLE 4 Risk factors for the development of hypophosphatemia.

Treatment with FCM[a]
Recurrent or ongoing blood loss: abnormal uterine bleeding[b], hereditary hemorrhagic telangiectasia, other gastrointestinal bleeding
Malabsorptive disorders: bariatric surgery, inflammatory bowel disease, celiac disease
Normal renal function
Severe iron deficiency
Lower body weight
Low baseline serum phosphate
Higher serum PTH

[a]Strongest risk factor for the development of treatment-emergent hypophosphatemia.
[b]Highest baseline risk for developing treatment-emergent hypophosphatemia.

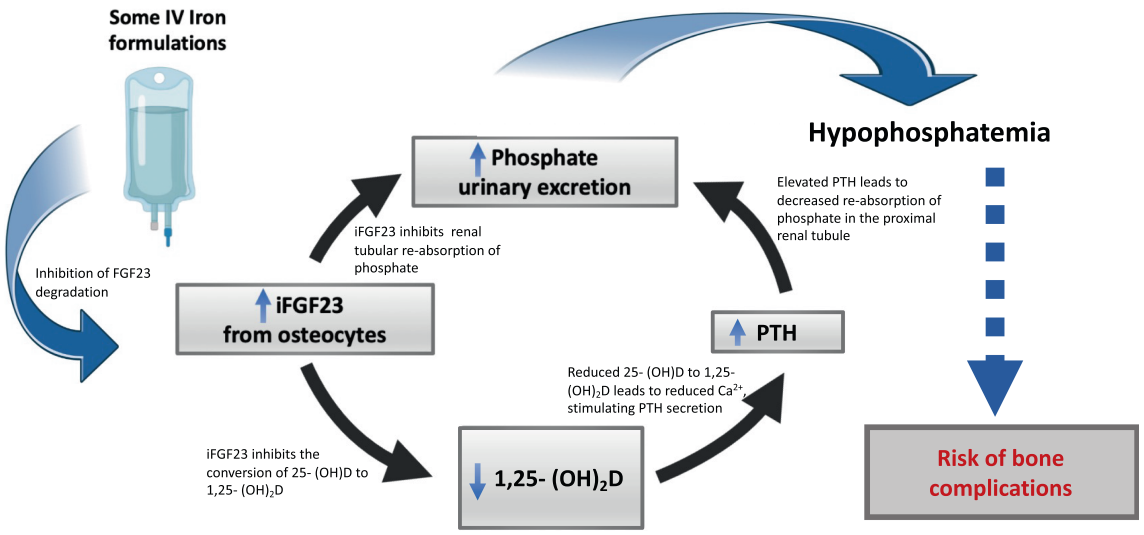

FIGURE 3 Mechanism of treatment- emergent hypophosphatemia, adapted from Blumenstein et al.[64] iFGF23, intact fibroblast growth factor 23. Following administration of some intravenous iron formulations there is a sharp rise in the plasma intact FGF23 (iFGF23) which triggers a pathophysiological cascade of renal phosphate wasting, calcitriol deficiency, and secondary hyperparathyroidism frequently culminating in hypophosphatemia even after iFGF23 levels have normalized.

8 | SUMMARY

IV iron is used in the management of a host of common ailments that lead to ID and IDA. These include persons with blood loss in which oral iron is insufficient to meet the demands of the losses (heavy menstrual bleeding, hereditary hemorrhagic telangiectasia), 2nd and 3rd trimester of pregnancy where oral iron does not keep up with the requirements of the growing fetus, states in which the absorption of iron is limited (post-bariatric surgery, inflammatory bowel disease), and other comorbid conditions with systemic inflammation and increased hepcidin (cancer and chemotherapy induced anemia, CKD). There is an abundance of data supporting the safety and efficacy of IV iron. Life threatening infusion reactions are extremely rare and concern for their occurrence should not be a barrier to the use of IV iron. In this manuscript, we have provided an expert consensus guideline to inform providers of best practices in the administration of IV iron formulations, management of infusion reactions and treatment-emergent hypophosphatemia.

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CONFLICT OF INTEREST STATEMENT

Layla Van Doren and Michael Auerbach have both received honoraris from Pharmacosmos Therapeutics for educational, non-promotional programs. Michael Auerbach has received research funding for data management only from Covis Pharma. Kristine Taylor is a speaking consultant for Pharmacosmos Therapeutics.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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