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Safety of intravenous iron following infusion reactions

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Safety of intravenous iron following infusion reactions

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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ABSTRACT

Background: Where an ongoing requirement for intravenous iron replacement exists after an index infusion reaction, current recommendations are limited to expert opinion and isolated case reports.

Objective: To evaluate the safety of recommencing an infusion or subsequent re-challenge following an infusion reaction to intravenous iron.

Methods: Infusion reactions to intravenous iron occurring between 1 January 2010 and 31 December 2019 at a metropolitan health network were identified. Patient characteristics, reaction type (mild, moderate or severe hypersensitivity, delayed, or Fishbane: transient flushing and truncal myalgias), and outcomes of recommencing the index infusion or subsequent re-challenge were examined.

Results: Among 13509 iron infusions, 195 infusion reactions occurred in 195 patients (1.4% of infusions). Recommencement of the index infusion (generally with a reduced infusion rate and pre-medication) was tolerated in 33/33 patients with Fishbane (20/20) or mild (9/9) and moderate (4/4) hypersensitivity reactions. Subsequent rechallenge (generally at standard infusion rates to an alternative formulation, ferric carboxymaltose) was successful in 68/69 patients with Fishbane (23/23), mild (26/26), moderate (16/17) and severe (3/3) hypersensitivity, or delayed (2/2) reactions. All 9 patients re-challenged to the original formulation (iron polymaltose) completed the infusion.

Conclusion: Following an infusion reaction to intravenous iron infusion, recommencement of the index infusion is safe for Fishbane or mild and moderate hypersensitivity reactions. Subsequent re-challenge to an alternative formulation is tolerated, including in severe hypersensitivity reactions (albeit based on limited

numbers). Where alternative formulations are not available, re-challenge to the same formulation could be considered, depending on the risk-benefit profile.

HIGHLIGHTS BOX**What is already known about this topic?**

- Hypersensitivity reactions of any severity to intravenous iron have a reported prevalence of less than 0.1%
- The majority of adverse reactions to iron are not immunological IgE-mediated responses

What does this article add to our knowledge?

- Recommencement of an infusion after transient flushing and truncal myalgias or mild and moderate hypersensitivity reactions to intravenous iron is safe
- Rechallenge to an alternative intravenous iron formulation following transient flushing and truncal myalgias or mild and moderate, single-system hypersensitivity reactions is safe

How does this study impact current management guidelines?

- Current guidelines are based on expert opinion and isolated case reports
- This study provides clinical guidance regarding the safety of recommencing an infusion or subsequent rechallenge following an adverse reaction to intravenous iron

Key words: Intravenous iron, drug reaction, iron polymaltose, ferric carboxymaltose, ferric derisomaltose, iron replacement, pre-medication

Abbreviations:

Nil

INTRODUCTION

Anaemia affects over 30% of the population globally, 50% of which is due to iron deficiency.^{1,2} Iron deficiency is the most common nutritional deficiency worldwide and, in contrast to other nutritional deficiencies, remains prevalent in developed countries.¹ In the hospitalized population, iron deficiency anaemia affects up to 41% of patients.³

Oral iron replacement is the primary treatment of iron deficiency anaemia. When oral formulations are not tolerated, deemed inadequate, or both, intravenous iron is indicated. Hypersensitivity reactions to iron infusion of any severity have a reported prevalence of less than 0.1%.⁴ Excluding high molecular weight iron dextran, the incidence of anaphylaxis to intravenous iron is 1 in 200,000.⁵ Comparing reaction rates between different intravenous iron formulations is hampered by sample size requirements; an estimated 6600 patients are needed to show a difference in reaction rates between two formulations.⁶

Most reactions to intravenous iron are not believed to be IgE-mediated, but the underlying mechanisms cannot easily be clinically distinguished.⁷ Complement-activation related pseudoallergy may be the most common mechanism, where activation of mast cells and basophils in blood is mediated by complement.⁸ Another reaction, characterised by transient flushing and truncal myalgias which resolves spontaneously after minutes, occurs in approximately 1-in-100 patients given intravenous iron. This self-limiting reaction is known as the 'Fishbane reaction'.^{7,9}

A history of hypersensitivity to intravenous iron has been reported to be a risk factor for further hypersensitivity reactions during subsequent intravenous iron infusions. Recommendations exist for risk mitigation and management of reactions to intravenous iron, with additional considerations for future treatment with intravenous iron where this is deemed necessary.^{4,7,10,11} The European Medicines Authority (EMA) recommends that a severe hypersensitivity reaction to intravenous iron is a contraindication to subsequent therapy with any intravenous iron formulation.¹¹ For mild and moderate hypersensitivity reactions, should treatment with intravenous iron be deemed necessary after risk-benefit analysis, it is suggested that the iron formulation responsible for the initial hypersensitivity reaction be avoided and an alternative used.⁷ However, there is a paucity of direct evidence regarding the basis for these recommendations. Other than case reports^{12,12} and a single retrospective review of 15 patients re-challenged to iron after a reaction,¹⁴ no studies to our knowledge have systematically examined recommencement of an index infusion following a hypersensitivity reaction, or subsequent re-challenge on another occasion.

We explored the feasibility and safety of administering intravenous iron following an adverse reaction to an initial iron infusion. We reviewed iron infusions at our institution resulting in adverse reactions and examined patients who underwent recommencement and completion of the index infusion. Where the infusion was not recommenced, we further examined those who underwent subsequent re-challenge to intravenous iron of the same or alternative formulation.

METHODS

Our health network, Alfred Health, comprises a tertiary academic centre and two nearby secondary centres. The pharmacy dispenses or prepares all iron infusions administered across the network. Pharmacy dispensing records were interrogated for all iron infusions administered during multi-day admissions or day admissions between 1 January 2010 and 31 December 2019. Adverse reactions occurring during or after iron infusion were identified from both discharge coding and reports to the network Adverse Drug Reactions Review Committee. This analysis was approved by our Institutional Review Board (ref: 87/20).

For patients experiencing adverse reactions, demographics, iron formulation, details of the reaction, and subsequent outcomes including re-challenge were recorded if performed at our network during the review period. We recorded all reported adverse reactions, whether occurring during or after the infusion and categorised them into five groups. Reactions consistent with a 'Fishbane reaction' were considered separately due to their distinct clinical syndrome and pathophysiology, transient nature and described association with intravenous iron. Immediate hypersensitivity reactions were stratified as mild, moderate or severe corresponding to Grades I-III of the Ring and Messmer grading system¹⁵. Delayed reactions, occurring after completion of the infusion, were also considered separately. Hence;

- (i) *Fishbane reaction*: Transient flushing and truncal myalgias
- (ii) *Mild hypersensitivity reaction*: Localised cutaneous manifestations

- (iii) *Moderate hypersensitivity reaction:* Reactions involving nausea or abdominal cramping, dyspnoea, hypotension or tachycardia, either in isolation or as part of a multisystem reaction
- (iv) *Severe hypersensitivity reaction:* Reaction involving bronchospasm, laryngeal oedema or shock, either in isolation or as part of a multisystem reaction
- (v) *Delayed reaction:* Reaction occurring post completion of the infusion.

We noted whether patients underwent re-commencement and completion of the index infusion or re-challenge on a subsequent occasion to either the same or an alternative iron formulation. Outcomes of re-commencements and re-challenges were specifically examined.

The rate of reactions was calculated from reactions detected relative to the total number of infusions administered over the ten-year period. Where an individual received more than one iron infusion over this period due to chronic causes of iron deficiency such as angiodysplasia or malignancy, each infusion was counted separately towards the total number of infusions.

RESULTS

There were 13,509 iron infusions in 11,130 patients over the ten-year period (Table 1). Whilst the vast majority of patients treated at our centre received only a single infusion of intravenous iron, a small proportion received up to 10 infusions during separate encounters over this period.

Iron polymaltose accounted for 7,896 infusions, ferric carboxymaltose for 4,710 and ferric derisomaltose (formerly iron isomaltoside) for 361.

Reactions to index infusions

Adverse reactions were reported in 195 (1.4% of all) infusions in 195 patients (Table 1). The reaction rate to iron polymaltose (2.2%) was higher than to ferric carboxymaltose (0.4%) or ferric derisomaltose (0.5%, $p < 0.001$). There were equal numbers of reactions occurring in admitted inpatients (97 reactions) and elective day patients (98 reactions). Among patients with reactions, the mean age of patients was 50 years (range 16-96) with a female predominance (66%).

Most reported (184 of 195; 94%) reactions occurred during the intravenous infusion, with only 11 reactions reported after the infusion (1 hour to 5 days). The 11 reactions occurring post-infusion all manifested as an exanthematous cutaneous reaction.

Fishbane reactions accounted for 59 (30%) reactions, occurring in 0.4% of all infusions. Mild hypersensitivity reactions accounted for 70 (36%) of 195 reactions, or 0.5% of infusions. Moderate reactions accounted for 48 (25%) reactions, or 0.3% of infusions and severe reactions in 7 (3%), or 0.05% of infusions. Delayed reactions occurring post completion of the infusion accounted for 11 (6%) of reactions, or 0.08% of infusions.

Urticaria was the predominant manifestation occurring in 79 (40%) of 195 reactions, followed by truncal myalgias in 59 (30%) of reactions. No patient experienced laryngeal oedema, shock or cardiorespiratory arrest. There were no fatal reactions in this cohort.

Re-commencement of index infusion

Of 184 patients who had infusions ceased due to an adverse reaction, 33 (18%) underwent re-commencement of the index infusion. All 33 successfully completed the infusion (Figure 1).

There were no differences in baseline patient characteristics among those who had their infusions re-commenced, compared to those who did not. The majority (27, or 82%) of infusions recommenced occurred prior to 2016, suggesting an evolution in clinical management over time. The strategy of recommencement was only pursued in patients who reacted to iron polymaltose.

Re-commencement was offered after Fishbane reactions in 20 patients (61%) and mild hypersensitivity reactions characterised by transient single-system

manifestations in 9 patients (27%). Four patients (12%) had their infusions recommenced after moderate single-system reactions involving abdominal cramping and nausea, transient hypotension or tachycardia. No patient had their infusion recommenced after reporting subjective dyspnoea. Re-commencement of the infusion was not offered to patients with severe reactions.

Of infusions re-commenced, the majority (31, or 94%) utilised a slower infusion rate. Twenty-three (70%) were pre-medicated with antihistamine, corticosteroid or both prior to re-commencement, five of whom had already received pre-medication prior to initial commencement of the infusion.

Re-challenge on a subsequent occasion

Of 151 patients who did not complete their initial infusion due to an adverse reaction, 69 (46% of reactions occurring during intravenous infusion) received re-challenge within our health network with intravenous iron on a subsequent occasion during the review period. The mean time from initial reaction to re-challenge was 297 days (range; 0 to 2,112 days).

There were no differences in baseline patient characteristics among those who were re-challenged compared to those who were not. The mean dose of iron at re-challenge was 1000mg compared to the mean dose at initial infusion of 1400mg.

Only patients who reacted to iron polymaltose were re-challenged. Rechallenge was undertaken with the same formulation (iron polymaltose) in nine patients (13% of re-challenges) and to an alternative formulation (ferric carboxymaltose) in 60 patients

(87% of re-challenges). Pre-medication was given prior to re-challenge in 61%, with either antihistamine, corticosteroid or both. Only three patients were re-challenged at a slower infusion rate.

Of 59 patients who had experienced a Fishbane reaction, 23 patients (39%) were re-challenged.

Of 70 patients who had experienced a mild hypersensitivity reaction, 26 patients (37%) were rechallenged. Of 48 patients who had experienced a moderate reaction, 17 patients (35%) were rechallenged including six patients whose initial reaction featured multisystem involvement.

Of seven patients who had experienced a severe reaction involving objective evidence of bronchospasm in all cases, three patients (43 %) were re-challenged, including one patient with multisystem involvement.

Of 11 patients who completed their initial infusion of iron polymaltose but reported a delayed exanthematous cutaneous reaction, two were rechallenged to an alternative formulation (ferric carboxymaltose). Neither received pre-medication or rate alteration during re-challenge.

Outcomes of re-challenge

Of 69 patients re-challenged after a reaction during the initial infusion, 68 (98%) patients tolerated completion of their challenge infusion without incident (Figure 1).

10/11 patients who had experienced moderate, single-system reactions tolerated re-challenge to an alternative formulation, namely ferric carboxymaltose. This included re-challenge following reactions manifest as isolated dyspnoea in seven patients, abdominal cramping and nausea in two patients and hypotension with tachycardia in one patient. Six patients re-challenged to an alternative formulation following a moderate reaction with multi-system involvement tolerated re-challenge, as did three patients re-challenged following severe reactions featuring bronchospasm in all cases with multi-system involvement in two patients.

Both patients re-challenged after a delayed reaction to intravenous iron occurring after completion of the index infusion were able to tolerate re-challenge with an alternative formulation.

Only one patient did not complete re-challenge, to infusion with ferric carboxymaltose, due to an immediate reaction characterised by chest tightness and nausea. This was following an initial moderate single-system reaction to iron polymaltose similarly manifesting as chest tightness with subjective dyspnoea. The re-challenge infusion was administered at standard rate without pre-medication.

One further patient reported transient facial flushing and urticaria two days after completing ferric carboxymaltose re-challenge, indicating a possible, albeit atypical, delayed reaction.

DISCUSSION

There is a high global prevalence of iron deficiency for which intravenous replacement may be clinically indicated, but adverse reactions can occur during these infusions. Faced with such an infusion reaction, how should clinicians proceed? In our cohort, recommencing the index infusion was tolerated when the reaction suggested mild or moderate hypersensitivity, or was consistent with a Fishbane reaction. Re-challenge on a subsequent occasion was also well-tolerated, including in a small group who had experienced severe hypersensitivity reactions (Table 2)

Our data supports previous recommendations to cautiously recommence infusions following a mild hypersensitivity reaction or Fishbane reaction to intravenous iron.^{7,10} In addition, recommencement was also successful in four patients following moderate single-system reactions (excluding dyspnoea).

We support the European Medicines Agency (EMA) recommendations that re-challenge with intravenous iron after an index reaction is considered in the context of individual patients' clinical requirements.¹¹ Our 98% rechallenge success rate to an alternative iron formulation supports the safety of this strategy, and builds on previously published case reports^{12,13} and guidelines based on low-quality evidence.¹⁰

Currently, the EMA recommends that patients with a severe hypersensitivity reaction to IV iron do not proceed to re-challenge.¹¹ However, in our cohort, six patients who experienced an initial moderate multi-system reaction and three patients who had experienced a severe reaction with objective bronchospasm also tolerated rechallenge to an alternative formulation, adding to previous published data.¹⁴ Our small numbers preclude a firm recommendation here, but our results suggest it is reasonable to consider rechallenge with an alternative formulation should a patient have a pressing need for IV iron replacement, as long as safety measures are in place.

All nine patients in the study rechallenged to the same iron formulation (iron polymaltose) after an initial Fishbane reaction, or mild and moderate single-system hypersensitivity reactions, tolerated the re-challenge. This is particularly relevant to areas where, due to resource limitations, only one intravenous iron preparation may be available.

When recommencing an intravenous iron infusion, our results suggest a reduced infusion rate and pre-medication may facilitate completion of the infusion and prevent progression to a more severe, life-threatening reaction.^{7,10} While evidence remains conflicting regarding the utility of H1 or H2 receptor antagonists, such antihistamine administration may provide symptomatic relief for localised symptoms including urticaria.¹⁰

When patients are re-challenged to intravenous iron after an initial reaction, our data suggests it may be unnecessary to routinely reduce the infusion rate. The need for a

slow infusion rate during re-challenge has previously been suggested based on its efficacy in preventing reactions to intravenous iron amongst patients with previous anaphylaxis to other medications.¹⁰ Other authors reported their use of a slow infusion rate during successful controlled re-administration of intravenous iron in 15 patients, but remained uncertain of its benefit.¹⁴ On a related note, pre-medication with antihistamine, corticosteroid or both occurred in 61% of successful re-challenges in our cohort, but its role in the outcome of re-challenge still requires prospective assessment.

Guidelines have suggested that a lower dose of iron be used for patients with previous non-life threatening reaction to intravenous iron.¹⁰ In our cohort, the mean dose at re-challenge (1000mg) was lower than the initial infusion (1400mg) but this was due to the 1000mg maximum dose for the most commonly utilised challenge formulation (ferric carboxymaltose). Amongst those re-challenged with the same formulation, dose reduction did not prove essential with all nine patients successfully re-challenged to the same formulation receiving either the same (6 patients) or higher dose (3 patients).

Safety of both recommencement of the initial infusion and re-challenge in appropriate patient groups was demonstrated in both an inpatient and elective day stay setting. We did not identify any baseline patient characteristics which influenced outcomes.

We acknowledge a number of limitations of our data. The prevalence of reactions to intravenous iron was higher than the reported prevalence of <0.1%. This may reflect

the inclusion of all reported reactions regardless of reaction severity or characteristics such as Fishbane reactions, estimated to occur at a higher frequency of 1 in 100,⁷ and self-reported symptoms such as dyspnoea without objective findings. Additionally, the retrospective nature of the study relies on all adverse drug reactions being documented (and thus coded), or reported to the Adverse Drug Reactions Review Committee.

Not all patients experiencing a reaction were re-challenged, whether due to adequate repletion of iron stores with oral therapy, resolution of the underlying cause for iron deficiency, clinician anxiety or patient death. Additionally, our study only included patients who underwent challenge at our centre for whom follow up was made possible by centralised pharmacy dispensing records, and it is possible that re-challenge occurred elsewhere. Only patients who reacted to an initial infusion of iron polymaltose were re-challenged in our cohort; we did not identify any re-challenges after reactions to ferric carboxymaltose or derisomaltose. This is likely reflective of the latter formulations having more recently entered clinical use. In addition, the majority of ferric carboxymaltose and derisomaltose infusions were performed in an elective day stay setting which may indicate higher overall patient health status and lower clinical requirement for intravenous iron replacement after a reaction.

In summary, recommencement of the index infusion or subsequent re-challenge appears to be safe in appropriate patient groups after an adverse reaction to intravenous iron. Re-commencement of the initial infusion using a slow infusion

protocol, with or without administration of antihistamines for symptomatic treatment, appears to be a safe approach following Fishbane reactions, or mild hypersensitivity reactions. It may also be reasonable to consider re-commencement of an infusion after moderate reactions if transient and affecting a single-system only.

Re-challenge with an alternative intravenous iron formulation was safely performed in the majority of patients in our cohort after Fishbane reactions and mild or moderate, single-system hypersensitivity reactions to intravenous iron. In our study, this strategy also proved safe in patients re-challenged after an initial moderate multi-system reaction or severe reactions featuring bronchospasm, however our patient numbers are insufficient to make an evidence-based recommendation for this latter group. Globally, where alternative intravenous iron preparations are not available, it may be reasonable to consider re-challenge to the same formulation following Fishbane reactions and mild or moderate, single-system reactions. Utilisation of a slow infusion protocol does not appear critical for successful re-challenge.

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FIGURE LEGENDS

Figure 1: Adverse reactions to intravenous iron infusion, clinical management, and subsequent outcomes.

Table 1: Reactions to intravenous iron over 10 years stratified by iron preparation and reaction severity.

	All preparations	Iron poly maltose	Ferric carboxy maltose	Ferric deriso maltose	p-value†
Total infusions, n	13,509	7,896	4,710	361	
Adverse reactions, n (%)	195 (1.4%)	176 (2.2%)	17 (0.4%)	2 (0.5%)	<0.00001
Baseline patient characteristics					
Total patients, n	195	176	17	2	
Age in years, median (IQR)	46 (31-69)	34 (28.5-48)	48 (31-73)	36.5 (NA)	0.09
Female, n (%)	129 (66%)	112 (64%)	15 (88%)	2 (100%)	0.07
Inpatient, n (%)	97 (50%)	96 (54%)	1 (6%)	0	<0.0001
Elective day stay, n (%)	98 (50%)	80 (46%)	16 (94%)	2 (100%)	
Median (IQR) prescribed dose, mg	1500 (1000-1500)	1000 (1000-1000)	1500 (1000-1500)	1500 (1500-1500)	0.0001
Premedication					
Any, n (%)	28 (14%)	27 (15%)	1 (6%)	0	0.62
Antihistamine, n (%)	28 (14%)	27 (15%)	1 (6%)	0	0.62
Corticosteroid, n (%)	22 (11%)	21 (12%)	1 (6%)	0	0.76
Both, n (%)	22 (11%)	21 (12%)	1 (6%)	0	0.76
Timing of reaction					
During infusion, n (%)	184 (94%)	168 (95%)	14 (82%)	2 (100%)	0.16
Post infusion, n (%)	11 (6%)	8 (5%)	3 (18%)	0	
Severity					Overall = 0.037
Fishbane, n (%)	59 (30%)	56 (32%)	1 (6%)	2 (100%)	0.006
Truncal myalgias	59	56	1	2	
Flushing	12	10	0	2	
Mild, n (%)	70 (36%)	62 (35%)	8 (47%)	0 (0%)	0.39
Urticaria	66	58	8	0	
Angioedema (non-laryngeal)	6	6	0	0	
Moderate, n (%) *	48 (25%)	44 (25%)	4 (23%)	0 (0%)	1.0
Urticaria	13	12	1	0	
Angioedema (non-laryngeal)	2	1	1	0	
Gastrointestinal	14	13	1	0	
Tachycardia	8	7	1	0	
Dyspnoea	22	21	1	0	
Hypotension	11	9	2	0	
Severe, n (%) **	7 (3%)	6 (3%)	1 (6%)	0 (0%)	0.52
Urticaria	0	0	0	0	
Angioedema (non-laryngeal)	2	1	1	0	
Gastrointestinal	1	1	0	0	
Tachycardia	2	2	0	0	
Dyspnoea	7	6	1	0	
Hypotension	0	0	0	0	
Bronchospasm	7	6	1	0	
Delayed, n (%)	11 (6%)	8 (5%)	3 (18%)	0 (0%)	0.16
Exanthematous cutaneous reaction	11	8	3	0	

*16 Patients in this category experienced multi-system manifestations

** 4 Patients in this category experienced multi-system manifestations

† p-values for differences between continuous variables were calculated using Kruskal-Wallis tests and differences between proportions were calculated using Chi-square or exact contingency tables

Table 2: Outcomes following recommencement or rechallenge by reaction type and severity.

Reaction type, N†	Re-commencement of index infusion, n (%)	Outcome	Re-challenge* on subsequent infusion, n (%)	Outcome	Neither re-commenced nor rechallenged, n (%)	Conclusions
Fishbane reaction N = 59	20 (33.9)	All tolerated	23 (39.0)	All tolerated 5 to same formulation (iron polymaltose) 18 to alternative formulation (ferric carboxymaltose)	16 (27.1)	Recommencement and rechallenge were both safe
Mild Hypersensitivity reactions N = 70	9 (12.9)	All tolerated	26 (37.1)	All tolerated 3 to same formulation (iron polymaltose) 23 to alternative formulation (ferric carboxymaltose)	35 (50.0)	Recommencement, and rechallenge to an alternative formulation, were both safe Rechallenge to the same formulation was tolerated in the small number who underwent this.
Moderate Hypersensitivity reactions N = 48	4 (8.3) After transient moderate, single-system reactions only	All tolerated	17 (35.4)	16 tolerated 1 to same formulation (iron formulation) after single-system reaction 9 to alternative formulation (ferric carboxymaltose) after single-system reactions 6 to alternative formulation (ferric carboxymaltose) after multi-system reactions 1 intolerant**	27 (56.3)	Recommencement was tolerated for single-system reactions (excluding dyspnoea) in the small number who underwent this. Rechallenge to an alternative formulation was generally safe, including for multi-system reactions.
Severe Hypersensitivity reactions N = 7	None	NA	3 (42.9)	All tolerated 2 to alternative formulation (ferric carboxymaltose) after single-system reactions 1 to alternative formulation (ferric carboxymaltose) after multisystem reaction	4 (57.1)	No data on recommencement Rechallenge to an alternative formulation was tolerated in the small number who underwent this.
Delayed Exanthematous Cutaneous reaction N = 11	NA	NA	2 (18.2)	All tolerated Both to alternative formulation (ferric carboxymaltose)	9 (81.8)	Rechallenge to an alternative formulation was tolerated in the small number who underwent this.

*Patients who underwent subsequent re-challenge represent a separate group of patients in whom re-commencement of their index infusion was not attempted

**Patient experienced immediate nausea and chest tightness to alternative formulation (ferric carboxymaltose) following moderate single-system reaction (chest tightness and dyspnoea) to index iron-polymaltose infusion

†N represents patient numbers

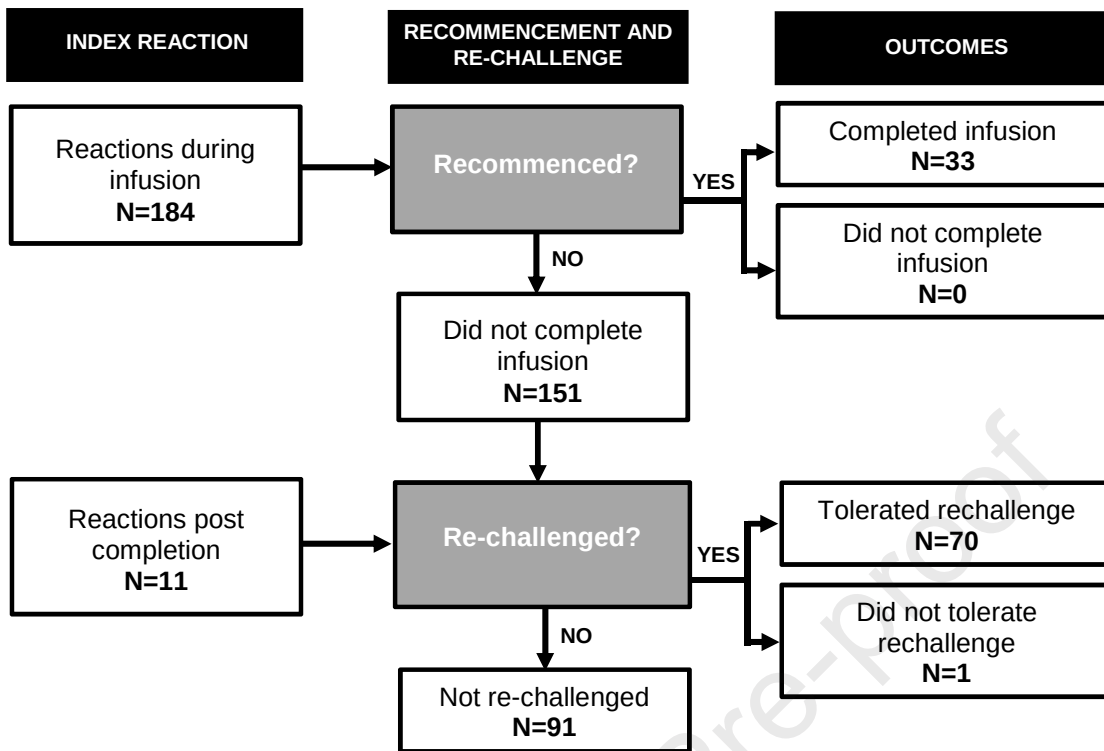


Figure 1