Alder Hey Children's NHS
NHS Foundation Trust

Reference Number: FOIAH2324/600
From: Commercial

Date: 26 January 2024

Subject: Iron Infusion and Iron Extravsation

Q1 How many iron extravasations have been reported within your organisation, if possible, could I have a 5- or 10-year breakdown?

A1 Zero

Q2 Do you know how often IV iron is given, prescribed and used within the organisation?

A2 There have been 175 doses prescribed in the last 999 days.

Both Venofer and Ferinject (IV iron products) have been prescribed electronically since 2019. IV iron supplements are calculated on the patients' weight and extent of iron deficiency. Infusions are prepared on the ward by trained nurses, and are administered over 30-90 minutes, depending on the preparation and dose. The Trust iron deficiency anaemia guidelines discuss this.

Q3 Are patients given any information leaflets/documents prior to infusion? May I have a copy?

A3 Information not held – we do not have leaflets/documents specific to infusions.

Q4 Do you have an iron infusion policy - May I kindly have a copy?

A4 See attachment - Iron Deficiency Anaemia Guidelines

IRON DEFICIENCY ANAEMIA GUIDELINES

1. SCOPE

These guidelines are intended for the treatment of Iron Deficiency Anaemia (IDA)

INTRODUCTION

Anaemia is a defined haemoglobin level below the standard reference ranges for the patient's age. It is a common side effect of chronic disease. In most cases it is a combination of chronic iron deficiency anaemia (IDA) and anaemia of chronic disease (ACD), both these types of anaemia are treated in the same way but the initial investigations performed are used to define whether the anaemia is IDA, ACD or a combination of the both.

Less commonly, anaemia can be caused by vitamin B12 or folate deficiency.

Iron deficiency can be challenging to treat as the daily absorption capacity of elemental Iron from the duodenum is approximately 10-20mg. Higher doses can exacerbate intestinal inflammation and poor absorption may necessitate the parenteral route.

2. DIAGNOSIS

Please refer to Appendix 1 for flow diagram on diagnosis and treatment.

In order to diagnose anaemia, the following initial investigations should be performed:

- Full blood count profile to include - Haemoglobin (Hb), haemocrit (Hct), mean cell volume (MCV) and mean cell haemoglobin (MCH)
- Iron studies to include – Iron, Transferrin, Ferritin and Transferrin saturation (Tfs)
- Inflammatory markers - C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR)

Any individual value cannot be taken alone to diagnose anaemia but in combination they can be used to identify clinically significant anaemia.

Important considerations when diagnosing:

Haemoglobin (Hb) is a strong indicator of Iron Deficiency Anaemia. Factors that can influence haemoglobin values include age, gender, race, pregnancy, altitude and smoking. Hb reference ranges differ depending on age.

Transferrin saturation (Tfs): The ratio serum Iron to Transferrin is called transferrin saturation. A Tfs of less than 16% generally indicates a diagnosis of IDA and should be considered alongside other diagnostic factors.

Typically, Hb, Hct, MCV, MCH, ferritin and TfS are low in children with IDA. Iron deficiency anaemia is defined as low Hb with other biochemical evidence of low iron stores. Hb alone shouldn't be used to diagnose IDA.

Serum ferritin is an accurate marker of total body iron stores in healthy subjects. However, it is also an acute phase protein and therefore may be falsely elevated in children with active inflammation. It has been suggested that serum ferritin levels less than 100 micrograms/L can be used as a cut off for Iron deficiency. If ferritin is high, this should be interpreted cautiously and in conjunction with the other inflammatory markers CRP and ESR. In ACD it would be expected that ferritin would be higher than usual.

MCV and MCH can be used in conjunction with other values performed as part of FBC to identify microcytic hypochromic anaemia (more common in Iron deficiency anaemia). It should be interpreted with caution in patients on azathioprine and other antimetabolites as these can elevate the MCV.

The limits for diagnosis of Iron deficiency have not been well defined. The following reference ranges have been identified in the literature and age-related reference ranges are quoted on laboratory reports:

Table 1. Limits for diagnosis of Iron deficiency for children < 18 months

Age group	Hb (lower limit in (g/L)	Hct (lower limit in (%)	MCV (lower limit of normal) (fl)	Ferritin (microgram/L)	Transferrin saturation (%) (lower to upper limit)
0-1 months	159	42	88	20-200	4.1-59
1-2 months	134	33	91	200-600	4.1-59
2-6 months	94	28	74	50-200	4.1-59
6-12 months	113	31	68	7-140	6.5-39
12-18 months	109	31	71	7-140	6.5-39

Table 2. Limits for diagnosis of Iron deficiency for children > 18 months

Age group	Hb (lower limit in [g/L])	HCT (lower limit in [%])	MCV (fl)	Ferritin (ug/L)	Transferrin saturation
18 months to 3 years	105	33	70-86	4-74	<16%
3 to 7 years	115	35	75-87		
7 to 13 years	115	35	77-94	11-93	
14 to 18 years, female	120	36	78-102	4-122	
14 to 18 years, male	130	3	78-98	10-98	

3. TREATMENT

The goal of Iron supplementation is to normalise haemoglobin levels and Iron stores. Aim for an increase in haemoglobin of at least 20g/L within 4 weeks of treatment.

Oral Iron Supplementation

Oral Iron should be considered for:

- Mild anaemia Hb ≥100g/L
- Clinically inactive disease
- No history of Iron intolerance

The recommended dose of oral elemental iron is 3-6mg/kg per day (maximum 200mg) in 2-3 divided doses. Refer to the most up to date version of BNFC for dosing information.

Doses should be rounded for ease of administration. At Alder Hey the following oral iron preparations are available:

(1) Sytron (Sodium Feredetate) containing 27.5mg elemental Iron in5mL
(2) Galfer (Ferrous Fumarate) containing 45mg elemental Iron in 5mL
(3) Ferrous sulphate 200mg tablets containing 65mg elemental Iron per tablet

Administration Details

Oral Iron is absorbed best on an empty stomach; however, administering with food reduces gastrointestinal side effects and therefore may be preferable to ensure treatment is tolerated. It is particularly important to avoid drinking tea around the time of oral Iron administration.

Side effects
Side effects of oral Iron include constipation and nausea. Patients and parents should be warned that stools may become black in appearance.

Intravenous (IV) Iron Supplementation

IV Iron should be considered if:

The patient has clinically active chronic disease, haemoglobin below 100g/L and they are clinically unstable

and at least one of the following applies:

- Absorption of oral Iron is unreliable
- Patient has an intolerance to oral Iron e.g. gastrointestinal upset
- Patient has an inadequate response to oral Iron

Oral Iron should be discontinued while patient is on IV Iron.

There are two formulations of IV Iron available for paediatric patients at Alder Hey.

(1) Ferinject® (ferric carboxymaltose) for all patients above 1 year of age
(2) Venofer® (Iron sucrose) for patients under 1 years of age or older children who cannot tolerate Ferinject.

Ferinject® allows the cumulative Iron dose to be given in fewer infusions and has shown to improve Hb levels faster than other IV Iron preparations.

Note: Venofer is unlicensed in under 18 years old but there is evidence to support use in children (see references).

Other Options:

Rarely, if a patient isn't responding to IV Iron, an erythropoietic agent (such as Neorecormon® (Epoeitin Beta)) may be indicated under the advice of haematology.

Ferinject® (Ferric Carboxymaltose) Monograph (500mg in 10mL)

Cautions:
Allergic disorders; eczema; hepatic dysfunction; immune conditions; infection (discontinue if ongoing bacteraemia); inflammatory conditions; oral iron should not be given until 5 days after the last injection; severe asthma; hypophosphataemia, Extravasation injuries can cause scaring and tattooing.

For Patients over 1 year old

Pre-dose Monitoring
All Patients should have iron studies, and phosphate levels done prior to initiating ferinject.

IV iron should not be given based on Hb alone.
If patient has phosphate less than 1mmol/L check

- Phosphate
- PTH
- Calcium
- vitamin d status
- urinary phosphate

Phosphate must be corrected prior to Ferinject infusion.
Phosphate level should be rechecked in all patients 1 week post ferinject infusion and corrected if appropriate – this may be done locally or at Alder Hey.

Phosphate Level	**Action**
<0.6mmol/L or symptomatic	Correct intravenously as per injectable medicines therapy guidelines
>0.6mmol/L and asymptomatic	Correct orally with phosphate Sandoz 2-3mmol/kg daily in 2-4 divided doses Re-check phosphate levels within 7 days
>1 mmol/L	No action needed

Dose:
The doses for children weighing more than 35kg are derived from the Summary of Product Characteristics for Ferinject®.
The maximum single dose recommended for individuals is 20mg/kg by IV infusion, not to exceed 1000mg by either route.
The maximum recommended cumulative dose of Ferinject® is 1000mg of iron per week.

In this guideline, the dose for children weighing less than 70kg is derived from those used in a small number of observational studies and from guidelines used at other centres, rather than the Summary of Product Characteristics (SPC).

Children under 70kg and under 14 years old:

15mg/kg (maximum dose should not exceed 750mg).

Children above 70kg and over 14 years old:

Prescribers should use the dosing table below to determine the appropriate dose:

Hb g/L	>70kg
<100	**Total dose 2000mg** Maximum single dose is 1000mg. This dose must be divided into two separate doses administered at least 1 week apart
100-140	**Total dose 1500mg** Maximum single dose is 1000mg. This dose must be divided into two separate doses administered at least 1 week apart
>140	**Total dose 500mg**

Doses should be rounded to the nearest 100mg and each single rounded dose must not exceed 20mg/kg given by short IV infusion.
Patients requiring a total dose > 1000mg must have their dose split to ≤1000mg with doses given at least a week apart.

Administration:
Ferinject® may be administered as an intravenous infusion over 15-30 minutes up to once a week.
Ferinject® should only be given via a large patent vein (either peripherally or centrally), due to the risk of extravasation and long-lasting skin staining.
If signs of infection are present, patient must have a medical review before administration.

Dose	Volume of 0.9% Sodium Chloride required for dilution prior to administration
100-200mg	50mL
200-500mg	100mL
>500mg to 1000mg	250mL

The reconstituted solution for injection should be visually inspected prior to use. Only use clear solutions without sediment.

Monitoring:
Patients should be closely monitored throughout the infusion and for at least 30 minutes afterwards for signs of infusion reaction. Baseline oxygen saturation, heart rate and blood pressure should be taken and repeated during infusion then at 30 minutes post infusion. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.
Additional treatment with antihistamines and/or corticosteroids should be given as appropriate

Phosphate to be checked 1 week after Ferinject® and corrected if needed.

There is evidence that demonstrates ferritin levels decrease rapidly 2-4 weeks following replacement and much more slowly thereafter, however this evidence showed that the mean ferritin levels did not drop to levels where retreatment may be considered during the 12 week follow up.

Venofer® (Iron Sucrose) Monograph

For patients under 1 years old or intolerant to Ferinject

Dose

Contact Pharmacy (Medicines.Information@alderhey.nhs.uk) for dosing schedule using the Ganzoni Formula below.

15mg/kg (max 500mg) + [weight(kg) x (target Hb-actual Hb (g/L)) x 0.24]

The **total** calculated correction should be given in divided doses of:

<40kg: 5mg/kg/once weekly (NB: this dose is higher than BNFc dosing)

≥40kg: 200mg once weekly

Or
3mg/kg 3 times weekly can be given in certain instances until total iron dose is achieved.

Administration:
A test dose is not required.
Dilute to a concentration of 1mg/mL with 0.9% sodium chloride and infuse over 90 minutes if 5mg/kg or 30mins if 3mg/kg.
(NB. this rate of infusion differs to the summary of product characteristics).
Venofer should only be given via a large patent vein (either peripherally or centrally), due to the risk of extravasation and long-lasting skin staining.

Facilities for cardiorespiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions must be available when IV Iron is administered.
Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

Monitoring:
Patients should be closely monitored for signs of infusions reactions throughout the infusion and for two hours afterwards. Baseline oxygen saturation, heart rate and blood pressure should be taken and repeated during infusion then at 30 mins post infusion.

If hypersensitivity reactions or sign of intolerance occur during administration, the treatment must be stopped immediately.

4. FOLLOW UP

Patients treated with IV Iron should be monitored to establish efficacy of treatment and for recurrent Iron deficiency. After successful treatment of Iron deficiency with intravenous Iron, re-treatment with either IV or oral Iron should be initiated as clinically appropriate. Prophylactic oral Iron supplementation may be considered clinically appropriate in some patients and, if initiated, should be regularly reviewed.

Haemoglobin and ferritin should be rechecked 4-8 weeks after initiating treatment to ensure response. Following this, monitor every 3 months for at least a year after correction and every 6 to 12 months thereafter. Blood tests will be taken either at Alder Hey, a local hospital or by the patient's GP - arrangements will depend on the individual patient's circumstances.

5. REFERENCES

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Appendix 1. Diagnosis and Treatment of Anaemia

Check Hb, MCV, MCH, ferritin, Iron studies (which includes iron, transferrin and transferrin saturation), CRP and ESR

- At Diagnosis
- Regular Follow ups
  - 6-12 monthly for chronic disease in remission
  - At least 3 monthly for active chronic disease

Iron Deficiency Anaemia (IDA)

- Hb <normal for age
- CRP/ESR: normal
- Tfs <16%
- Ferritin <normal for age

IDA and Anaemia of Chronic Disease (ACD)

- Hb <normal for age
- CRP/ESR: elevated
- TfS <16%
- Ferritin ≤normal range for age

IDA and ACD (in IBD patients)

- Hb <normal for age
- CRP/ESR: elevated
- TfS <16%
- Ferritin ≤normal range for age

Commence Iron Therapy Treatment
Reassess disease periodically (using PUCAI, PDCDAI and other biochemical markers to assess inflammation)
Evaluate IBD treatment to achieve remission
Consider:

- Vitamin B12/Folate Deficiency
- Drug induced (e.g. sulfasalazine, thiopurines)
- RBC disorders and haemoglobinopathies

If the above has been excluded, consider review by Haematology

Oral Iron

Indicated if:

- Hb ≥100g/L
- IBD in remission (mild disease)
- Patient preference

(See below for preparation and dose)
Re-evaluate Iron studies in 4-8 weeks and if increase of Hb <20g/L consider IV therapy

Intravenous Iron Therapy

Indicated if:

- Severe IDA, Hb <100g/L
- Moderate to severe disease activity
- Need for rapid response
- Intolerance to oral Iron
- Suboptimal response to oral Iron (increase of <20g/L in 4-8 weeks)
- Patient preference

Re-evaluate Iron studies in 4-8 weeks and if suboptimal response re-evaluate disease status and re-consider IV Iron

Blood Transfusion

Indicated in:

- Acute bleeding
- Hb <70g/L and rapid increase is warranted due to significant cardiorespiratory compromise

<1 years old - VENOFER

>1 years old - FERRINJECT

Contact Medicines Information for dosing schedule
Calculate Iron required (mg):
15mg/kg (max 500mg) + [weight(kg)x(target Hb-actual Hb(g/L))x0.24]

Max dose: 5mg/kg/week (NB. this dose is higher than BNFc dosing)

Under 70kg and under 14 years old:
15mg/kg (maximum 1000mg)

Hb g/L	>70kg over 14 years old
<100	**Total dose 2000mg** Maximum single dose is 1000mg. This dose must be divided into two separate doses administered at least 1 week apart
100-140	**Total dose 1500mg** Maximum single dose is 1000mg. This dose must be divided into two separate doses administered at least 1 week apart
>140	**Total dose 500mg**

IRON DEFICIENCY ANAEMIA GUIDELINES	
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Review and Revision(s) Log *Record of revision(s) made to guidelines since Version 1*			
Section Number	Page Number	Revision(s) made	Reason for revision(s)
		Age range updated	Change in licensing
3.	2	Dose of oral elemental iron is 3-6mg/kg per day (max 200mg) in 2-3 divided doses	As per BNFC
	1	Removal of Inflammatory bowel disease Addition of cautions to ferinject monograph Amendment of dosing table Change units of Hb Addition of phosphate monitoring	Make guideline available for general use For safety For clarity Reflects Meditech reporting of Hb Reports of hypophosphataemia
	4, 6[1,12],7		Slightly ambiguous for patients over 35kg (max single dose is 20mg/kg - if iron required > that should be split into two doses).

	4	Ferinject dose for children <35kg	Change to dosing recommendations of Ferinject for children <35kg
	5	Ferinject age changed to reflect new licensing Ferinject max dosing changed to reflect licensing Add comment 'if signs of infection for medical review before administration'	*Children and adolescents aged 1 to 13 years* A single Ferinject administration should not exceed: • 15 mg iron/kg body weight • 750 mg of iron (15 mL Ferinject) The maximum recommended cumulative dose of Ferinject is 750 mg of iron (15 mL Ferinject) per week. If the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose