LRI Children's Hospital

Iron Chelation Therapy For Iron Overload in Patients With Haemoglobinopathy & Inherited Anaemia

Staff relevant to:	Paediatric haematology teams, paediatric medicine, paediatric intensive care.
Approval date:	November 2022
Revision due:	April 2026
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Version:	2
Trust Ref:	C65/2022 (Previously E3/2019)

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1. Introduction and who this guideline applies to

This document aims to offer clinical guidance regarding iron chelation therapy for paediatric patients with transfusional iron overload. The majority of these patients are receiving regular red cell transfusion for inherited anaemias.

Cases need to be assessed individually and management tailored appropriately. If in doubt, please seek the opinion of the paediatric haematology team.

Guidelines are based on:

- BSH Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias

2. Iron overload and chelation therapy

2.1 General Principles

- Iron overload primarily occurs secondary to red cell transfusion as the body does not have an efficient mechanism to excrete iron. It can occur in non-transfusion dependent thalassaemia due to increased gastrointestinal absorption.
- Significant iron accumulation can occur in the heart leading to cardiac failure, the liver resulting in cirrhosis and can cause endocrinopathy.
- Iron chelation therapy is an effective treatment modality to aid iron excretion and reduce morbidity and mortality from iron overload but requires accurate monitoring and treatment adherence.

2.2 Monitoring for iron overload

- Monitoring for iron overload is critical to identify complications and assess treatment efficacy.
- Patients at risk of iron overload should be assessed for iron overload and the relevant complications as part of their annual review. These patients include those:
    - On regular transfusion every 3 months or less
    - Non-transfusion-dependent thalassaemia
    - Non-transfused rare inherited anaemias
- Ferritin levels broadly correlate indirectly with iron burden and trends over time are useful to monitor. However ferritin is an acute phase protein and so there can be significant variability with levels.
- Ferriscan MRI liver and T2* cardiac MRI allow quantification of tissue iron within the liver and heart respectively. This should be used alongside trends in ferritin level to guide treatment decisions regarding chelation therapy.
- Ferritin should be measured between 1-3 monthly to identify trends.
- MRI of the heart and liver to assess iron loading should be performed in transfused children as soon as they are able to lie in a scanner or sooner under sedation if concerns regarding severe iron overload.

- Surveillance MRI scans to assess cardiac and liver iron overload should be performed at regular intervals on transfused children as per Appendix 1.
- Monitoring of liver iron accumulation is primarily with Ferriscan MRI and the role of liver biopsy is now limited.
    - Long-term liver iron concentrations above 7mg/g dry weight is associated with increased risk of fibrosis
    - Iron concentrations above 15mg/g dry weight are associated with increased risk of myocardial iron overload
- Cardiac T2* MRI is the gold standard investigation for iron accumulation within the heart.
    - T2* values less than 20ms are associated with increased myocardial iron
    - T2* values less than 10ms are associated with an increased risk of developing cardiac failure
    - Left ventricular ejection fraction should be assessed annually by echocardiography or MRI from 8yrs old for patients receiving regular top-up transfusions
- The rate of iron loading (ROIL) from transfusion can be calculated to review chelation doses and this should be done annually.
    - ROIL=(units of blood transfused x 200) / (weight x days over which blood administered)
    - ROIL=(ml of blood transfused x 1.08) / (weight x days over which blood administered)

2.3 Starting iron chelation therapy

- The timing of when to start chelation therapy is important as if it is introduced too early it carries the risk of over-chelation but equally if it is left too late when there is accumulation in the endocrine system, it can be difficult to reverse the damage.
- For patients with sickle cell disease receiving top-up transfusion and transfusion-dependent thalassaemia patients, chelation should start:
    - after 10-12 transfusions or 100ml/kg/year of packed red cells OR
    - when serum ferritin >1000µg/L on 2 occasions
- For patients with non-transfusion dependent thalassaemia, chelation should start if:
    - ferritin is above 800µg/L OR
    - liver iron concentration is above 5mg/g/dry weight
- For patients with non-transfusion dependent rare inherited anaemia, the need for chelation should be individualised based on their condition and iron loading.
- The choice of chelation agent according to age for transfusion dependent patients is listed in the table below:

Table 1: Chelation agent options

Age	Initial chelation option	Alternative chelation option	Cautions
Under 2yrs	Desferrioxamine 20-40mg/kg/day 3-5 nights/week 8-12hrs sc infusion	Deferasirox-FCT 7-21mg/kg/day (unlicensed indication)	Desferrioxamine avoid dose >40mg/kg/day Deferasirox monitor ALT & renal function
2yrs & under 6yrs	Desferrioxamine 20-40mg/kg/day 5 days/week 8-12hrs sc infusion	Deferasirox-FCT 14-28mg/kg/day once daily	Desferrioxamine avoid dose >40mg/kg/day monitor closely in renal impairment and reduce dose/frequency of administration Deferasirox monitor closely if creatinine clearance <60ml/min & avoid if <30ml/min avoid in severe liver impairment Deferiprone avoid if history of recurrent neutropenia monitor for agranulocytosis or neutropenia
Over 6yrs	Deferasirox-FCT 14-28mg/kg/day once daily	Desferrioxamine 30-40mg/kg/day 5 days/week 8-12hr sc infusion Or Deferiprone 75-100mg/kg/day (unlicensed indication for sickle cell & rare anaemias)	

- Desferrioxamine 50-60mg/kg five days a week or deferasirox-FCT at 21mg/kg/day will achieve negative iron balance in most patients with an average rate of iron loading (ROIL = 0.3-0.5mg/kg/day).
- Iron chelation therapy should be reviewed every 3 months to review efficacy and to assess for complications and compliance with treatment.
- When iron overload is not controlled with monotherapy:
  - Cases should be discussed in regional EMSTN Haemoglobinopathy MDT
  - Combination therapy or switching to alternative agent, such as deferipone, should be considered based on individual cases based on the site and severity of iron loading, the history of compliance, prior toxicity and patient choice

- The current BCSH guideline should be used as a reference point Shah - 2022 - British Journal of Haematology - Wiley Online Library Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias (b-s-h.org.uk)

Table 2: Monitoring for complications of iron chelation

	Deferasirox	Deferipone	Desferrioxamine
Prior to starting	Creatinine, ALT, urinalysis	FBC, Creatinine, ALT	FBC, Creatinine, ALT
Month 1	Weekly Creatinine & urinalysis. ALT fortnightly	Weekly neutrophils	
Month 2 onwards			
ALT	Monthly	Monthly	Monthly
Creatinine	Monthly	Monthly	Monthly
Urinalysis	Monthly		
Neutrophil		Weekly for 12 months then 2-4 weekly	
Audiometry	Annual from age 5 years	6-12 monthly if used in combination only	Annual from age 5 years
Opthalmology	Annual from age 5 years	6-12 monthly if used in combination only	Annual from age 5 years
Growth			Height 3 monthly 6-12 monthly annual sitting & standing height
Other	Rate of iron loading	Zinc level	Rate of iron loading Zinc level Therapeutic index = mean daily dose (mg/kg)/ferritin (µg/l); aim to keep <0.0025

3. Education and Training

Regular teaching is provided on ward 27, specialist trainees regional training days and nursing training days.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Transfusion spread sheets	3 monthly clinical review of patient and spread sheets	Dr Kaljit Bhuller	3 monthly	Seen by haemoglobinopathy team/data manager
Annual review	12 monthly documented annual review includes iron chelation category	Dr Kaljit Bhuller	12	See by haemoglobinoapthy team/data manager

5. Supporting References

1) BSH Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias

6. Key Words

Iron overload, chelation, transfusion, thalassaemia, sickle cell

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

Contact and review details	
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Details of Changes made during review: Written internal guideline in line with BSH guideline published 2021 Tables for choice of chelation therapy, monitoring for complications of therapy and monitoring for iron overload Changed from Trust category E to C guideline	

Appendix 1. Monitoring for complications of iron overload

	Routine test	Frequency	Notes
Iron load and distribution	Serum ferritin	1-3 monthly	
	MRI cardiac T2* & LVEF (baseline by age 8 & thereafter)	2 yearly Annually 6 monthly	>20ms 10-20ms <10ms
	Liver ferriscan or T2* (baseline by age 8 & thereafter)	1-2 yearly Annual 6-12 monthly	1.8-7mg/g dry weight >7<15mg/g dry weight >15mg/g dry weight
Endocrine	Height/weight Pubertal status Oral glucose tolerance test Thyroid function Morning cortisol Gonadal function	6 monthly Annual Annual Annual Annual Annual	Until adult height From age 10 From puberty From age 10 if family history of diabetes Patients with diabetes
Bone	Vitamin D Bone density scan	Annual 2 yearly	From age 2 From puberty
Cardiac	<u>Good chelation</u> Cardiology review ECG Echo MRI cardiac T2*/LVEF <u>Poor chelation</u> Cardiology review ECG Echo MRI cardiac T2*/LVEF	 1-2 yearly Annual Annual See above 3-6 monthly 3-6 monthly 6 monthly 6-12 monthly	 From age 16 See above See above
Liver	LFTs Hep C Ab, Hep B sAg & Hep B core Ab Ultrasound Liver iron assessment	Monthly Annual 6 monthly See above	 In patients with cirrhosis See above
Other tests	Soluble transferrin receptor	Annual	Low levels relative to iron loading may indicate high cardiac risk