bjh guideline

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

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Methodology

This guideline was compiled according to the BSH process at https://b-s-h.org.uk/guidelines/proposing-and-writing-a-new-bsh-guideline/. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature review details (Appendix 1)

A literature review was conducted on 28 September 2018. Databases searched included MEDLINE (OVID) from 1 January 1960 to 28 September 2018 and Cochrane Database. A top-up search was conducted on 28 October 2020 to cover 29 September 2018 to 28 October 2020.

Search terms were deferoxamine, deferasirox, deferiprone, thalassaemia major, transfusion, Diamond-Blackfan anaemia, and sickle cell disease. One additional paper that was missed in the searches was extracted based on author expertise. Filters were applied to include only publications written in English, randomised and non-randomised clinical trials, longitudinal cohort studies, comparative studies, meta-analyses, multicentre studies, observational studies, reviews, systematic reviews, validation studies, human and *in vitro* laboratory evidence with synergy indices and published between 01 January 1960 and 28 October 2020.

Review of the manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee General Haematology, the BSH Guidelines Committee and the General Haematology sounding board of BSH. It was also on the members section of the BSH website for comment. It has also been reviewed by the UK Thalassaemia Society and Sickle Cell Society; these organisations do not necessarily approve or endorse the contents.

Introduction

Iron overload (IOL), resulting from regular or intermittent blood transfusions or from increasing dietary iron absorption can cause serious and life-threatening complications. Patients at risk of IOL include those with inherited anaemias such as transfusion-dependent thalassaemia (TDT) and non-transfusion-dependent thalassaemia (NTDT), transfused sickle cell disease (SCD) and rarer anaemias such as congenital sideroblastic anaemia (CSA), congenital dyserythropoietic anaemia (CDA), Diamond-Blackfan anaemia (DBA) as well as red cell enzymopathies, membrane disorders and defects in haem synthesis pathways. The United Kingdom has approximately 15 000 patients with these disorders and diagnosis and management of IOL is important in minimising morbidity and mortality. Other disorders that are associated with IOL such as hereditary haemochromatosis or acquired anaemias such

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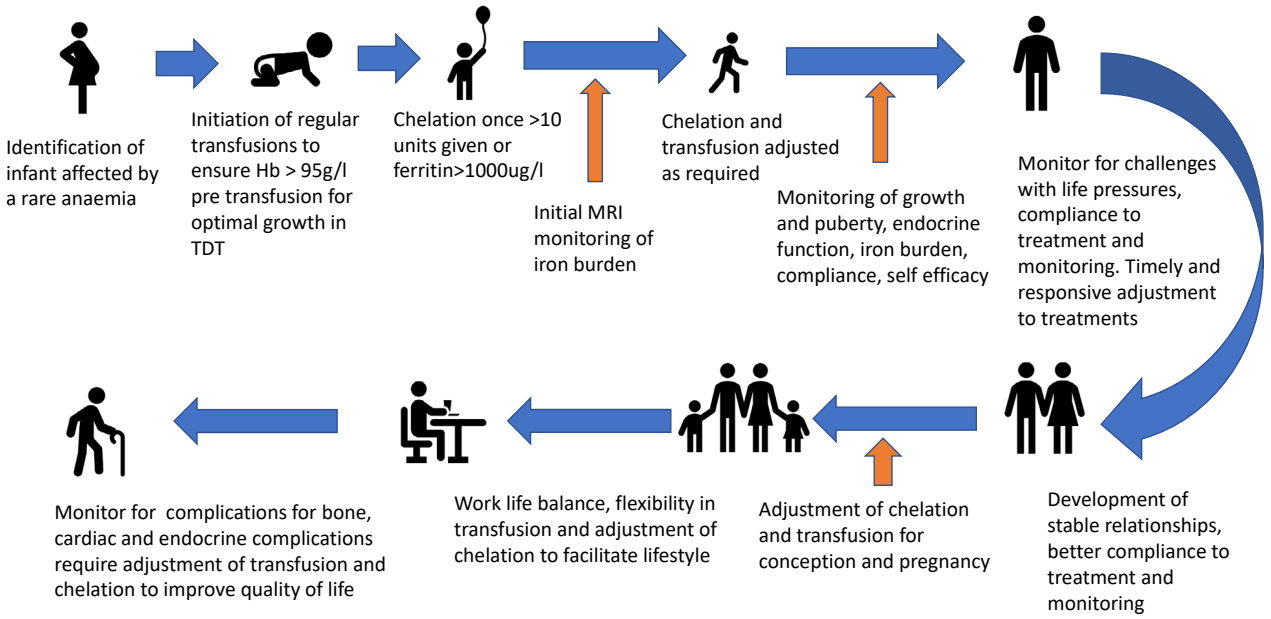

Fig 1. Lifetime triggers for treatment modification in transfused patients.

as the myelodysplastic syndromes are not covered by this guideline.

The extent and severity of IOL is affected by both the underlying disorder and the intensity and duration of transfusion. Patients on regular top-up transfusions are at most risk whilst those on intermittent transfusions develop IOL more slowly. In the absence of blood transfusion, sickle cell disorders tend not to accumulate excess iron: however, manual and automated exchange transfusion may result in mild degrees of IOL or even iron deficiency.[1–3]

Patients with NTDT and non-transfused rare inherited anaemia (NTRIA) may develop IOL through sporadic transfusions or from chronically increased gastrointestinal (GI) iron absorption. Iron accumulation from transfusion in TDT is on average about 40-fold faster (0.4 mg/kg/day)[4] than from GI iron absorption in NTDT (0·01 mg/kg/day).[5] Increased GI iron absorption is less well recognised in the NTRIA syndromes and often missed; however, the pathophysiological relationships between anaemia and iron absorption are similar to that in NTDT.[6,7]

Over a lifetime, transfusion-dependent patients will require changes to iron chelation regimes depending on the severity of IOL, side effects of chelation agents and lifestyle issues such as preparation for or during pregnancy (Fig 1). Monitoring for IOL and concordance with chelation therapy are the key to successful clinical outcomes. Regular monitoring of IOL informs both patients and clinicians about the effectiveness of chelation as well as sites of organ loading, allowing early intervention to control the iron burden.

Complications of iron overload

Most complications of IOL can be prevented or reversed before irreversible damage and dysfunction occurs.[8–10] Iron distribution is determined by the underlying disease and the route and kinetics of iron loading, as well as chelator regime, dose and adherence.

In general, transfusional IOL will begin in the macrophage system of liver, spleen and bone marrow and then progress to liver hepatocytes. As the liver iron concentration (LIC) increases, transferrin saturation increases, with non-transferrin-bound plasma iron (NTBI) appearing above 70% saturation. NTBI accelerates iron deposition in endocrine organs and ultimately the heart (Fig 2).[11]

Clinically significant IOL can occur early in young children with ineffective or absent erythropoiesis, such as DBA, CDA, and TDT. Patients with transfusion-dependent DBA are more likely to develop severe IOL compared to other transfusion-dependent patients,[12,13] with a greater propensity of myocardial IOL and higher NTBI levels.[14] Some CDA-1 patients may have concurrent therapy with interferon to limit blood transfusion. With suboptimal or absent chelation, myocardial IOL and endocrine complications can occur at an early age.[15–20]

Complications in NTDT are typically delayed due to slower iron accumulation rates, resulting in lower toxicity of iron species. LIC can be a surrogate marker for risk of other complications including hypogonadism, hypothyroidism, osteoporosis, thrombosis and pulmonary hypertension. NTDT patients with IOL are also at higher odds of developing renal dysfunction and iron may be implicated in direct tubulointerstitial and glomerular dysfunction.[21]

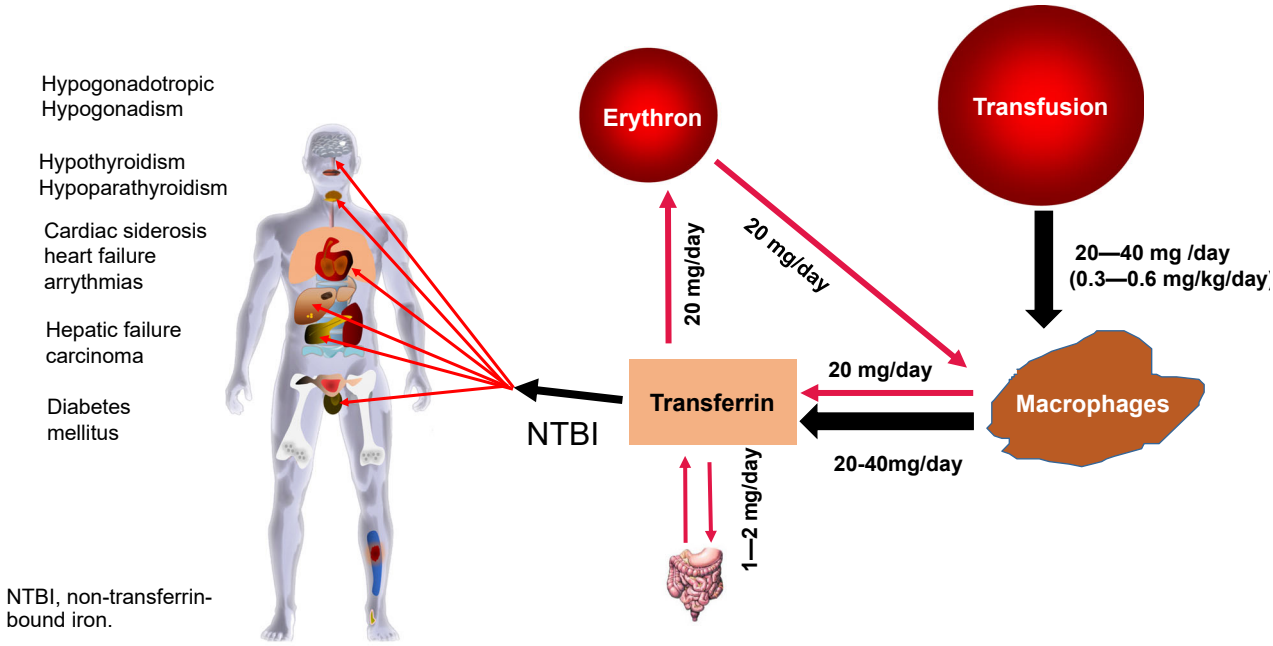

Fig 2. Iron loading and distribution in transfusion-dependent patients. The addition of blood transfusion increases iron for recycling by 20–40 mg/ day. Transferrin once saturated > 70% will result in the development of NTBI which causes end organ.

In TDT, myocardial IOL is more likely when transfusion iron loading rates significantly exceed the iron utilisation by the bone marrow.[22] In the absence of transfusion, myocardial IOL is rare even with high LIC. In NTDT the pattern of periportal hepatocellular iron distribution may explain the association with hepatocellular carcinoma (HCC) even in hepatitis C-negative patients.[19,23,24] Complications from IOL in NTRIA syndromes are less well described but assumed to be similar to NTDT. CSA and other metabolic iron disorders may develop IOL with normal or mildly raised serum ferritin levels.[25]

Without transfusion SCD patients are not typically iron-overloaded and indeed may be iron deficient due to urinary loss from intravascular haemolysis.[3] Children with SCD receiving top-up transfusions can rapidly develop liver IOL, but extra-hepatic involvement is unlikely if transferrin saturation and NTBI levels remain low.[3,26–28]

Recommendation

Patients at risk of iron overload (those on regular transfusions every three months or less, NTDT and NTRIA) should be assessed for iron overload and complications of iron overload as part of the annual review (1B). The frequency of scanning is detailed in Table I.

Cardiovascular complications

Cardiac iron deposition can manifest as arrhythmias or heart failure (HF). Accumulation of iron in the early stages can be asymptomatic but should prompt intensification of chelation.

Arrhythmia

Several tachycardias have been described secondary to IOL such as atrial fibrillation (AF) and ventricular tachycardia (VT), but bradycardia and heart block may also be seen. VT is a grave indicator of heart dysfunction requiring urgent and expert assessment.

Atrial arrhythmias do not always indicate severe cardiac iron toxicity and are increasingly evident in older patients, even when cardiac iron, as assessed by magnetic resonance imaging (MRI), has been normal for decades.

Heart failure

Acute, decompensated heart failure. Acute HF is now rare, but has a high immediate mortality risk, approaching 50%. The risk of HF increases as T2* falls below 10 ms. Patients with a cardiac T2* <6 ms have a >50% risk of developing HF within 12 months.[29] Regular Cardiac MRI (CMR) T2* and left ventricular ejection fraction (LVEF) measurements (frequency described in Table I) are critical for identifying patients who require timely escalation of chelation intensity (frequency and/or dose). Acute HF may be preceded by a small fall in LVEF.[30]

Chronic heart failure. Although recovery of LV function with chelation is the expected outcome for those who

Table I. Monitoring for complications of transfusional iron overload.

	Routine test	Frequency	Notes	Quality and grade
Iron load and distribution	Serum ferritin	1–3 monthly		1C
	MRI cardiac T2* and LVEF (baseline by age 8 and thereafter)	Two-yearly	>20 ms	1C
		Annual	10–20 ms	1B
		Six-monthly	<10 ms	1B
	Liver R2 (Ferriscan) or T2* (baseline by age 8 and thereafter)	Done concurrently with cardiac T2*	Liver iron quantification using T2* must be assessed using the same calculation and cross validated for results to be comparable	1B
		1–2 yearly	1.8–7 mg/g dry weight	1C
		Annual	>7<15 mg/g dry weight	1C
		6–12 monthly	>15 mg/g dry weight	1C
Endocrine	Height/Weight	6 months	Until adult height	1B
	Pubertal status[$]	Annual	From age 10	1B
	Oral glucose tolerance test	Annual	From puberty	1C
			From age 10 if family history of diabetes	1B
	Thyroid function	Annual	Patients with Diabetes and those on hormone replacement therapy 3–6 monthly	1B
	Morning cortisol	Annual		1B
	Gonadal function	Annual		1B
Bone	Vitamin D	Annual	From age 2	1C
	Bone density scan	2 yearly	From puberty	1B
Cardiac	Good chelation			
	Cardiology review	2 yearly/ Annual	from age 16	1C
	Electrocardiograph (ECG)	Annual		1C
	Echocardiogram (Echo)	Annual		1B
	MRI cardiac T2* and LVEF	as per Table 1	As per iron load and distribution recommendation	1B
	Poor chelation			
	Cardiology review	3–6 monthly	Baseline when poor chelation identified as per cardiologist recommendations	2C
	ECG	3–6 monthly		2C
	Echo	6 monthly		1B
	MRI cardiac and LVEF	6–12 monthly	As per iron load and distribution recommendation	1B
Liver	Liver function tests	Monthly		2C
	Anti-HCV, HbsAg, anti HB core Ab	Annual		1C
	Ultrasound	6 monthly	in patients with cirrhosis	1B
	Liver iron assessment	6 monthly to 2 yearly	As per iron load and distribution recommendation	1B
Other useful tests	Soluble transferrin receptors	yearly	low levels relative to transfusional loading may indicate high cardiac risk	2C

Anti HCV, Anti Hepatitis C Antibody; HbsAg, hepatitis B surface antigen; Anti HB core Ab, Anti hepatitis B core Antibody.
$Delayed puberty. No pubertal changes in girls by age 13 and boys by age 14.

survive acute decompensation, a small number of patients have long-term impaired ventricular function. This may be due to coincidental dilated cardiomyopathy, unrelated to IOL, or follow a viral myocarditis. Restrictive cardiomyopathy may also occur. Pulmonary hypertension and right-sided heart failure may be seen more commonly in NTDT and post splenectomised TDT. Rarer diseases should be excluded in atypical presentations or with an

inadequate response to conventional therapy with chelation and HF medication.

Valve disease is approached conventionally, and successful heart surgery has been undertaken in thalassaemia patients.

Hepatic complications

The pattern of liver siderosis and damage is determined by cellular iron distribution. Unbound iron species lead to cellular necrosis and eventual hepatic fibrosis, which can progress to cirrhosis especially when LIC exceeds 7 mg/g dry weight. The risk of progression can be reduced by adequate control of LIC with chelation.[31,32] Liver complications including HCC are becoming more prominent in older patients with TDT, NTDT and SCD. Coexisting hepatitis or non-siderotic liver disease will impact on liver damage and complications.

Endocrine and bone complications

Iron-mediated endocrinopathy may manifest as hypogonadotropic hypogonadism, growth retardation, hypothyroidism, hypoparathyroidism, growth hormone deficiency, diabetes mellitus and hypoadrenalism.[33–35] These complications are less common in patients receiving early regular chelation. Inadequate chelation can influence the rate of new-onset endocrinopathy and the likelihood of reversal.[36,37] Damage to the pancreatic islet cells leads to impaired glucose tolerance and diabetes. Increasingly, malabsorption due to iron-mediated damage to the exocrine pancreas is being recognised.

Thalassaemic bone disease has a complex pathobiology. In TDT, bone turnover is particularly high and iron is thought to encourage bone resorption by favouring osteoclast differentiation and inhibiting osteoblast activity. Reduced hepcidin levels are thought to contribute towards this process.[38]

Miscellaneous

Iron may cause adipose tissue remodelling leading to a pseudoxanthoma elasticum-like clinical syndrome.[39] IOL is also a risk factor for vasculopathy[40] and malignancies such as HCC and papillary and follicular thyroid carcinoma.[41,42]

Monitoring for iron overload

Monitoring for IOL is important in identifying existing complications, quantifying the risk of and therefore preventing future complications from developing.

Functional parameters of end-organ damage have been the mainstay of monitoring IOL (Table I). However, quantification of IOL allows organ-specific measurement of iron in the heart, liver, pancreas and pituitary and may identify high-risk patients before end-organ damage occurs.

Serum ferritin is important in quantifying overall risk of complications and is most useful for long-term trends.

Patients should be reviewed at least annually to ensure that IOL is monitored and end-organ damage assessed.

Ferritin

Serum ferritin broadly correlates with body IOL and its assessment can be performed frequently. However, ferritin is an acute-phase protein and may increase due to tissue damage and inflammation and is supressed by ascorbate deficiency. Ferritin is also affected by individual chelation drugs.[43] The relationship between ferritin and iron stores is similar in TDT and transfused SCD[44] provided serum values are taken several weeks away from a vaso-occlusive sickle crisis[45] but in NTDT, ferritin may underestimate the degree of IOL.[46]

Long-term control of ferritin with desferrioxamine therapy has prognostic significance[47] and maintenance of the ferritin below 2 500 μg/l is associated with a lower risk of cardiac disease and death.[30,33,48,49] Maintenance of ferritin below 1 000 μg/l may be associated with additional advantages in TDT.[8,33,50]The ferritin trend can be used as a guide for modifying chelation dosing but can be unreliable at high values (>3 000 μg/l). While low ferritin can identify patients at risk of over-chelation, ascorbate deficiency secondary to severe IOL may make this unreliable.

Rate of iron loading (ROIL) from transfusion

The ROIL in mg/kg/day can be calculated from the number of units given over a measured time period. Patients with average ROIL (0·3–0·5 mg/kg/day) will require average doses, whereas those with ROIL less than 0·2 mg/kg/day or greater than 0·5 mg/kg/day will require dose adjustment accordingly.[4]

$$\text{Rate of iron loading(mg/kg/day)} = \frac{\text{units of blood transfused} \times 200}{\text{Weight} \times \text{days over which the blood was administered}}$$

$$\text{Rate of iron loading(mg/kg/day)} = \frac{\text{ml of blood transfused} \times 1.08}{\text{Weight} \times \text{days over which the blood was administered}}$$

Tissue iron quantification

Liver iron. Methods for tissue iron quantification include liver biopsy and various MRI approaches. Historical data from LIC measurements from biopsies has shown that the severity of IOL impacts on the risk of developing complications. Long-term LICs above 7 mg/g dry weight have been associated with increased risk of fibrosis and above 15 mg/g dry weight with increased risk of myocardial IOL.[51,52] Liver biopsies have procedure-associated risks and the distribution of iron in the liver may be inhomogeneous.[53,54] Liver biopsies are now undertaken only where histology will contribute to management.

Magnetic resonance imaging typically measures signals from water hydrogen and this is perturbed by factors in addition to

storage iron. Three magnetic time constants can be generated: T2*, T2 and T1. High tissue iron leads to short time constants, which are hard to measure reproducibly. Several approaches have been validated for both cardiac and liver iron assessment including T2* [55,56], R2 (Ferriscan ®)[57] or R2*.[58]

LIC values where possible should be assessed using the same methodology (T2*, R2 or R2*) sequentially for the patient as the values for LIC do not concur across different techniques for data acquisition and analysis. There may also be considerable inter-centre variability even if the same methodology is being used to acquire the data.[59]

Transfusion-dependent patients should be having tailored MRI assessments of LIC routinely with a frequency dependent on the severity of iron burden, the intensity of chelation and the concordance with iron chelation therapy[60,61]

Cardiac iron. Cardiac T2* is the current standard measure for assessing myocardial iron deposition and T1 mapping is being used in research settings. T1 mapping makes rapid iron quantification easier for heart and liver and can be done in as little as six minutes.[62,63]

Cardiac T2* values less than 20 ms are associated with increased myocardial iron and T2* less than 10 ms is associated with an increased risk of developing cardiac failure.[29]

Other organs: pancreas, pituitary. Strategies to measure pancreas and pituitary iron using MRI are not as yet widely applied and their relevance in adult populations is not clear as iron-mediated damage is frequently already present. These strategies therefore remain research-based.

Recommendations

Monitoring recommendations for patients at risk of iron overload (those on regular top-up transfusions every three months or less, SCD on regular top-up transfusion, manual exchange or on automated apheresis with progressive rise in serum ferritin, NTDT and NTRIA):

- **Patients should have transfusional iron loading per year calculated annually (1B).**
- **Ferritin should be measured between one- to three-monthly intervals for trends (1C).**
- **MRI assessment:**
  - **a Initial MRI of the heart and liver to assess iron burden should be undertaken in transfused patients who have never had assessment and in children as soon as they are able to lie in a scanner without sedation (generally before the age of eight years) (1B).**
  - **b MRI of heart and liver for iron overload can be undertaken with sedation if there is clinical evidence to suggest severe iron overload in very young children who are not able to undergo MRI assessment without sedation.**
  - **c Surveillance: MRI for assessment of cardiac/liver iron should be performed at regular intervals on transfused adults and children. The frequency is described in Table I (1B).**
- **Cardiac assessments:**
  - **a LVEF should be assessed annually either by echocardiography or MRI from age 8 in patients receiving top-up transfusions (1B).**
  - **b Patients presenting with palpitations should be assessed for cardiac arrhythmias (1B).**
- **Liver assessments:**
  - **a Patients over the age of 40 should be assessed for liver fibrosis (2B).**
  - **b Patients who have had severe liver iron overload, previous hepatitis C or fibrosis should be screened six monthly for HCC with ultrasound (2B).**
- **SCD:**
  - **a Patients on regular top-up transfusions should have liver MRI assessments on a similar schedule to TDT and a cardiac MRI undertaken if the liver iron is above 15 mg/g/dry weight (1B).**
  - **b Patients on manual exchange and automated apheresis should have liver iron MRI based on consistently rising ferritin trends (2C).**
- **NTDT:**
  - **a NTDT (non-transfused) patients should have liver MRI assessment if ferritin is above 800 μg/l at baseline (1B).**
  - **b NTDT patients with previous IOL or who are receiving iron chelation therapy should have regular liver MRI assessment as the ferritin is unreliable (1B).**
- **NTRIA:**
  - **a NTRIA patients should have a baseline liver and cardiac MRI assessment if ferritin is >1 000 μg/l (1C).**
  - **b NTRIA patients with defects in the iron metabolism or haem pathway should be considered for MRI assessment if the ferritin is >500 μg/l or sooner if there are features to suggest IOL on clinical examination (1C).**
- **Poor compliance with chelation therapy should prompt earlier scans if needed (1B).**

Treatment of iron overload

Actions of chelating drugs

Chelation is an effective treatment modality, shown to decrease the risk of cardiac, endocrine and liver complications

of IOL and to improve overall survival in TDT. The purposes are two-fold:

1. To bind iron and to excrete the iron–chelate complex at a rate equal to or greater than the iron accumulation rate.
2. To decrease free radical-mediated tissue damage while the process is taking place.

Chelation typically decreases storage iron in the liver faster than from other tissues such as the heart. Thus, removal of pre-existing heart iron (when T2* is <20 ms) may lag behind that of the liver. By contrast, plasma NTBI is decreased rapidly by chelation, but this effect is transient, rebounding immediately after a chelator is cleared from the circulation.

While iron chelation has been highly successful in reducing morbidity and mortality from IOL this requires consistent adherence to treatment, which in turn depends on health care resources and the availability of clinical expertise to support, inform and encourage patients long-term.

Licensed chelating drugs and formulations

Three chelating drugs are licensed for treatment of IOL. Detailed descriptions of the individual pharmacology and toxicology of chelating agents are extensively described elsewhere.[64–67]

Desferrioxamine was the first drug licensed for transfusional IOL and has to be administered subcutaneously or intravenously.

Deferiprone is rapidly absorbed by the oral route and is given as a tablet, typically in three divided doses daily due to its rapid metabolism and elimination from plasma.

Deferasirox is administered orally once daily as it has a long plasma half-life. The original formulation was a tablet dispersed in a glass of water prior to ingestion (deferasirox-D). This has now been replaced by a film-coated tablet (deferasirox-FCT) formulation that is better absorbed and tolerated.[68–70] Due to enhanced absorption, doses need to be adjusted downwards by 0.7 × those previously recommended for the dispersible formulation.

Indications for treatment

Standard treatment. This depends on the underling diagnosis, the patient's age, the ROIL and the current body iron load and distribution. Iron excretion must generally match the ROIL to prevent body iron accumulation. Standard chelation doses are generally required for average ROIL; typically, 0.3–0.5 mg/kg of iron/day in TDT.

SCD patients receiving exchange transfusions generally have lower or neutral iron loading rates compared with 'top-up' transfusion regimes, so lower doses may be adequate should iron chelation be required[3] In rarer transfusion-dependent anaemias, iron excretion shows similar dose relationships to those of TDT and doses should be matched to ROIL.[71] As with TDT, the risk of cardiac and other extra-hepatic iron deposition is high when erythropoietic activity is low relative to the ROIL.[22] Patients with DBA often have higher ROIL and low iron utilisation by the bone marrow and need careful assessment before escalation to higher doses.[12,13,72]

For NTDT, the ROIL is an order of magnitude slower than for TDT, so lower doses are generally sufficient unless high levels of body iron have already accumulated.[73] Patients with NTDT and NTRIA may tolerate venesection if haemoglobin values are reasonable; a good example of this is CDA-1 patients maintaining reasonable haemoglobin values with interferon therapy. However, some patients with NTRIA may have significant IOL with more severe anaemia and patients with CDA, pyruvate kinase deficiency and CSA are highest risk. They may require intermittent short episodes of chelation every few years to maintain safe total body iron.

Timing of starting chelation

Guidelines and licensing for age of starting therapy vary somewhat between countries (but are based on the same data).[74] In principle, the risks of over-chelation increase if chelation is started too early but conversely once iron has accumulated in the endocrine system it can be difficult to reverse the organ damage. Unfortunately, data are limited about the safety of starting chelation in children or adults before transfusion has been ongoing for 2 years or before ferritin has reached 1000 μg/l. UK recommendations are to begin after 10–12 units of packed red blood cells (RBC), >100 ml/kg/annum of packed RBC (pRBC) (Hct 0.6), or ferritin >1,000 μg/l.[60,74,75] These recommendations are primarily based on experience with desferrioxamine.

In NTDT, chelation should be initiated following MRI assessment if the ferritin is above 800 μg/l or LIC >5 mg/g/dry weight.[5] NTRIA should be assessed on a disease and individual basis and chelation considered if there is evidence of IOL (ferritin >500 μg/l or LIC >5 mg/g/dry weight).

Recommendations

- **TDT patients should be commenced on iron chelation therapy after 10–12 transfusions or when the serum ferritin >1 000 μg/l on two occasions (1B).**
- **NTDT patients should be offered iron chelation therapy if ferritin is above 800 μg/l or liver iron is above 5 mg/g/dry weight (1A).**
- **NTRIA patients should be assessed on a disease and individual basis and chelation therapy or venesection (if Hb is adequate) considered if there is evidence of IOL (ferritin > 500 μg/l or LIC > 5mg/g/dry weight) (2C).;**
- **SCD patients receiving top-up transfusions should be commenced on iron chelation as per TDT patients (1B).**

- **SCD patients on exchange transfusion programmes should be offered iron chelation therapy on an individualised basis according to the type of exchange and the severity of the existing iron overload as measured by liver iron MRI assessment (2C).**

Dosing and frequency of monotherapies

Dosing, adjusted to the level of IOL and to the ROIL, is critical to both the efficacy and the safety of chelation therapy. Monitoring for complications of chelation should be as outlined in Table II and chelation regimes to be considered as outlined in Tables III and IV.

Standard monotherapy

Iron excretion depends on the frequency and dosing of chelation. Intermittent high doses in regularly transfused patients are not a satisfactory alternative to regular monotherapy, as this leads to iron-mediated free-radical damage between chelation episodes. Net response to chelation at any given dose also decreases as the iron loading rate increases so that required doses are likely to be higher at higher iron loading rates.[4] Although ROIL varies considerably between disorders and patients, the relationship between dose and iron excretion is essentially the same across disorders.[71]

Desferrioxamine doses of 40 mg/kg five days a week have been used, but these are often insufficient to promote a negative iron balance. Thus at average ROIL in TDT (0.3–0.5 mg/kg/day) only 65% of patients will be in negative iron balance, whereas at 50–60 mg/kg five days a week this rises to 86% of patients.[4] Due to potential desferrioxamine toxicities (growth and audiometry) children should not receive a mean daily dose exceeding 40 mg/kg. Adults generally tolerate 50 mg/kg well. Mean daily doses should be adjusted downwards as ferritin values fall in line with the therapeutic index.

Dosing is also critical to response with deferasirox: thus while over 80% of TDT patients with average ROIL respond to daily deferasirox-FCT at 21 mg/kg/day (deferasirox-D 30 mg/kg), this falls to just over half of patients at 14 mg/kg (deferasirox-D 20 mg/kg/day).[4] Adjustment in doses should be done in line with ferritin trends and LIC values as well as the presence of any derangement in serum creatinine and transaminase levels.

The relationship of dosing to iron balance with deferiprone is less clear as long-term LIC trends show considerable inter-study variation, reflecting the heterogeneity of dosing schedules, ROIL, baseline LIC values, and follow-up periods.[76–78] Unlike desferrioxamine, the response to deferiprone depends on baseline LIC; thus at 75 mg/kg/day, a negative iron balance was achieved in less than a third of patients overall but in 50% of patients where baseline LIC exceeded 9 mg/g dry weight.[79]

Recommendations

- **Children <6 years old should initially be offered sub-cutaneous desferrioxamine infusions. If there is failure to comply with desferrioxamine, then deferasirox should be started as soon as possible to prevent worsening IOL (1C).**
- **Patients above the age of six years starting on deferiprone must be informed of the risk of agranulocytosis and monitoring requirements (1B).**
- **The starting dose of monotherapy should be guided by the ROIL for desferrioxamine and deferasirox.**

Table II. Monitoring for complications of iron chelation.

	Deferasirox	Deferiprone	Desferrioxamine
Prior to starting	Duplicate, creatinine, ALT, urinalysis	FBC	FBC
		Creatinine, ALT	Creatinine, ALT
Month 1	Weekly creatinine and urinalysis	Weekly neutrophils	
	ALT fortnightly		
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 (over 5)
Ophthalmology	Annual from age 5 years	6–12 monthly if used in combination only	Annual (over 5)
Growth			height 3 monthly
			6 monthly to annual sitting/standing height
Other	Transfusional rate of iron loading	Zinc level	Zinc level
			Transfusional rate of iron loading
			Calculate therapeutic index*

ALT, alanine aminotransferase; FBC, full blood count.
*Therapeutic index. Mean daily dose (mg/kg)/ferritin (μg/l. Aim to keep <0.025 at all times).

Table III. Chelation options according to age cohort transfusion dependant patients.

Age	Ferritin threshold	Initial chelation option	Alternative chelation options	Contraindications and cautions
Under 2 years	Ferritin >1000 μg/l or 100 ml/kg blood transfused	Desferrioxamine 20–40 mg/kg/day 3–5 nights/week 8–12 h SC infusion.	Deferasirox-FCT 7–21 mg/kg/day (unlicensed indication)	Desferrioxamine Avoid dose >40 mg/kg/day in children Deferasirox Monitor closely for ALT and renal function in children
2 years and under 6 years	—	Desferrioxamine 20–40 mg/kg/day 5 days /week 8–12 h SC infusion.	Deferasirox-FCT 14–28 mg/kg/day OD	Desferrioxamine Avoid dose > 40 mg/kg/day in children Monitor closely in renal impairment and reduce dose /frequency of administration
Over 6 years	—	Deferasirox- FCT 14–28 mg/kg/day OD	Desferrioxamine 30–40 mg/kg/day 5 days/week 8–12 h SC infusion or Deferiprone* 75–100 mg/kg/day	Deferasirox Monitor closely if creatinine clearance (CrCl) is <60 ml/min and consider dose reduction Avoid if CrCl <30 ml/min. Avoid in severe hepatic impairment. Deferiprone Avoid if history of recurrent neutropenia.
Adults	—	Deferasirox-FCT 14–28 mg/kg/day OD	Desferrioxamine 40–60 mg/kg/day 8–24 h SC infusion or Deferiprone 75–100 mg/kg/day	Avoid in hypersensitivity to the active substance Monitor for agranulocytosis or neutropenia. Avoid doses > 100 mg/kg/day
Second line therapy for patients failing to respond to monotherapy regimes				
Adults and Children	—	Any of the combinations below based on patient prior tolerability and compliance Desferrioxamine and Deferiprone Initiate at appropriate dose of Desferrioxamine for age and cardiac iron burden. Deferiprone to start at 50–75 mg/kg/day then dose increases based on side effects and severity of IOL. Deferasirox and Desferrioxamine Initiate at appropriate dose of Desferrioxamine for age and Deferasirox-FCT at 14 mg/kg/day. Dose escalation of Deferasirox at regular intervals based on side effects and tolerability. Deferasirox and Deferiprone Add into the existing oral regime and start the new oral agent at its standard initial dose (14 mg/kg/day Deferasirox or 75 mg/kg/day Deferiprone). Consider a BID regime of both agents if needed to support compliance.	As above for individual agents Aim for optimised doses for each agent Check compliance to therapy and document

*Unlicenced indication for SCD and transfused rare inherited anaemia patients.

Desferrioxamine 50–60 mg/kg five days a week, or deferasirox-FCT at 21 mg/kg/day (deferasirox-D 30 mg/kg) will achieve negative iron balance in most patients with an average rate of iron loading (0.3–0.5 mg/kg/day) (1B).

- **Patients on deferiprone monotherapy should have doses adjusted up to a maximum of 100 mg/kg/day in three divided doses if the ferritin is not reducing provided the patient is fully compliant with administration (1B).**
- **Iron chelation therapy should be reviewed every 3 months to review efficacy, and to assess for complications and compliance with treatment (1C).**
- **Combination therapy should be considered when IOL is not controlled with monotherapy (1A).**

Table IV. Chelation options non transfusion dependent patients.

Age	Ferritin threshold	Initial chelation option	Alternative chelation options	Contraindications and caution
Above 6 years of age	>800 µg/l or liver iron > 5 mg/g/dryweight	Deferasirox-FCT 7–28 mg/kg/day	Desferrioxamine 20–40 mg/kg/day on 3 to 5 days a week depending on severity of iron burden or Deferiprone* 75–100 mg/kg/day in 3 divided doses (unlicensed indication)	Desferrioxamine Avoid dose >40 mg/kg/day in children Deferasirox Monitor closely if CrCl is <60 ml/min and consider dose reduction Avoid if CrCl <30 ml/min. Avoid in severe hepatic impairment. Deferiprone Avoid if history of recurrent neutropenia. Avoid in hypersensitivity to the active substance Monitor for agranulocytosis or neutropenia. Avoid doses >100 mg/kg/day

*Unlicenced indication for NTDT, SCD and NTRIA patients.

Treatment intensification

This is required when liver iron has accumulated to concentrations where liver damage may develop (>7 mg/g dry weight) or when myocardial iron has accumulated to abnormal levels (T2*<20 ms).

Emergency intensification is required when there is evidence of cardiac decompensation (LVEF <56%) or there is a high risk of this occurring (T2* <8 ms).

Monotherapy intensification

Without decreasing ferritin trends, particularly when baseline ferritin levels exceed 4 000 µg/l, serial measurement of LIC is recommended as LIC decreases in about half of such cases where ferritin is not deceasing.[80] The first consideration is to evaluate whether the patient is taking treatment at the prescribed frequency and dose. Iron balance may be improved by better concordance or by increased dosing. With treatment intensification, serum ferritin (and ideally LIC) must be followed closely to avoid over-chelation and its attendant side effects (see below). If increased dosing or frequency of chelation is not tolerated, the patient may require switching to an alternative regime.

Recommendation

Patients who fail to achieve negative iron balance despite adherence to optimal doses of monotherapy or patients who develop dose-limiting toxicities should be considered for combination therapy (1C).

Intensification with combination therapies

The term 'combination therapy' has been used for the various ways in which any chelators can be combined (true combination or sequentially). While combinations are not recommended as first line, these can be useful:

1. To increase overall exposure to iron chelation when monotherapy at licensed doses is insufficient.
2. When dose-dependent toxicity limits monotherapy.
3. When compliance with monotherapy at the required frequency is inadequate.
4. When simultaneous combination has the potential to synergistically increase cellular iron removal rates.[81]

Specialist advice should be obtained from the haemoglobinopathy coordinating centres prior to commencing combination therapy.

Desferrioxamine + deferiprone. As negative iron balance is achieved in only about 1/3 of patients receiving 75 mg/kg deferiprone,[82] desferrioxamine can be added to improve iron excretion. Desferrioxamine/deferiprone combination therapies

Table V. Chelation options for myocardial iron overload.

Cardiac T2*	Ejection fraction	Intensification therapy
8–20 ms	Normal	On Desferrioxamine Intensify Desferrioxamine dose and/or frequency. Switch SC to IV. Consider adding in one of the following • Deferiprone 75–100 mg/kg/day • Deferasirox-FCT 14–28 mg/kg/dayOn Deferasirox Intensify dose to 21–28 mg/kg/day, if no improvement or patient compliance suboptimal Consider following options: adding in one of the following • Desferrioxamine (40–60 mg/kg/day on 5–7 days a week) • Deferiprone 75–100 mg/kg/dayOr consider switching to: Monotherapy with Deferiprone at 75–100 mg/kg/day if the liver iron is below 5 mg/g/dry weight On Deferiprone: Optimise dose to maximum 100 mg/kg/day Consider adding in one of the following • Desferrioxamine (40–60 mg/kg/day) on 5 to 7 days a week • Deferasirox 14–20 mg/kg/day on 7 days a week
< 8ms	Normal	First line Desferrioxamine 50–60 mg/kg/day and Deferiprone 75 to 100 mg/kg/day Preference must be given to IV regimes. If unable to tolerate above regime, then consider one of the following with preference given to IV regime: Desferrioxamine (50–60mg/kg/day) + Deferasirox (21–28mg/kg/day) or Desferrioxamine (50–60 mg/kg/day) + Deferiprone (75–100 mg/kg/day)
< 20 ms	Abnormal – outside the normal values Acute Heart Failure Cardiac arrhythmia	IV Desferrioxamine – 24 h infusion (50–60 mg/kg/day) Add in Deferiprone 75 mg/kg/day once stable cardiovascular status (provided no previous complications such as agranulocytosis) or if unable to tolerate Deferiprone due to side effects consider adding in Deferasirox 14–28 mg/kg day

have been used for many years with evidence from randomised studies supporting efficacy,[83,84]

Desferrioxamine + deferasirox. Combinations of deferasirox and desferrioxamine are also effective and well tolerated. Aydinok *et al.*[85] showed a reduction in ferritin of 44% and 52% in LIC, with an increase in cardiac T2* of 33% in a prospective study of 60 patients with severe hepatic and cardiac IOL.

Deferiprone + deferasirox. This is potentially a highly effective combination[81,86] and although experience is relatively limited, at least one randomised study shows that this combination is highly effective, particularly improving cardiac T2*.[87]

Recommendation

- **Patients on iron chelation therapy should be monitored for concordance and side effects of treatment (II) (1B).**
- **The selection of iron chelation therapy (Tables III and IV) should be determined by the site and severity of IOL, together with history of compliance and prior toxicity and patient choice (1B).**

Management of iron overload in complex patients

Emergency treatment for reduced LVEF

This is potentially reversible but for best results deterioration in LVEF needs to be identified before the patient develops overt HF. Acute HF is a medical emergency requiring admission. Arrhythmias, particularly AF and,VT are encountered; if device therapy is needed then MRI-safe devices placed on the right side can permit ongoing cardiac iron measurement. Experience over two decades shows that continuous infusion of desferrioxamine can reverse HF.[88] Addition of deferiprone to this regime is recommended[89] based on a randomised

study where greater improvement in LVEF was seen in patients where deferiprone was added (Table V)[84].

- IOL-related acute HF is a medical emergency requiring intravenous desferrioxamine (50–60 mg/kg) as a continuous 24-hour infusion with no interruption in therapy. Deferiprone (75–100 mg/kg/day) should be added to this regime dependent on previous exposure and associated side effects. (1B)

Renal failure

In renal failure, desferrioxamine is cleared from the plasma by the liver but not ferrioxamine, which can be removed by peritoneal[90] or haemodialysis.[91] The risk of desferrioxamine toxicity may increase if doses are not adjusted. There is also increased risk of infections such as mucormycosis. Regimens include desferrioxamine intravenously during dialysis or desferrioxamine subcutaneously at reduced doses, three times a week between dialysis sessions.

Deferasirox is contra-indicated if the creatitine clearence is < 60ml/min and should be dose-reduced when renal function is deteriorating. A small proportion of patients can develop renal Fanconi syndrome as evidenced by renal tubular acidosis and hypophosphataemia prompting dose reduction or interruption.[92] Deferasirox may be appropriate in patients already on dialysis as the drug and iron complex are eliminated hepatically although peak concentrations may be elevated (>150 μm).[93] Case reports have shown feasibility with chronically transfused patients, for example with a starting dose of deferasirox-D at 15 mg/kg and using reducing doses as serum ferritin values fell progressively.[92,94]

Deferiprone has been shown to not accumulate in renal impairment.[95]

Recommendations

Low-dose desferrioxamine and/or deferiprone can be used in patients with chronic kidney disease (CKD) prior to dialysis (2C).

Once dialysis is initiated any of the chelators may be used in low doses with close monitoring for toxicity (2C).

Liver failure

Liver fibrosis and cirrhosis are encountered increasingly in older patients with long-standing IOL. Anecdotal experience using desferrioxamine in SCD has led to improved liver function even in patients with hepatic disease. Desferrioxamine may benefit liver function both by rapidly scavenging free radicals as well as more slowly decreasing storage iron. Deferasirox has been shown to stabilise or reverse liver fibrosis in IOL[31] but is contraindicated in patients with severe hepatic impairment (Child–Pugh class C) and should be used with caution in Childs–Pugh class B. All three chelators can be considered in patients with raised transaminases and Child–Pugh Class A hepatic impairment.

Conclusion

IOL is a cause for serious morbidity and mortality which is preventable with appropriate monitoring and chelation therapy. All patients on regular transfusion regimes (adults and children by the age of eight years) have an MRI assessment for cardiac and liver iron burden. Patients who are not regularly transfused but have rare inherited anaemias are at increased risk of IOL from both treatment of episodic anaemia and increased gastrointestinal iron absorption. In many cases they suffer from a poorer quality of life and life expectancy due to unrecognised IOL. Such patients should be under specialist services and have annual monitoring for IOL and related complications, to improve health outcomes. In the UK the development of Networks of Care (local and specialist haemoglobinopathy teams, haemoglobinopathy coordinating centres and the national haemoglobinopathy panel) will help improve clinical outcomes and standardise monitoring.

Failure of optimisation of IOL has multiple causes, which include clinical teams failing to monitor and prescribe appropriate doses of chelation therapy and also include significant patient factors such as failure to attend for monitoring assessments and suboptimal compliance with iron chelation due to side effects or a lack of awareness of the long- and short-term sequelae of IOL. These issues can be addressed by better engagement with patients and more education and support of both patients and clinical teams.

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Conflict of interests

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. FS declares advisory board (Silence therapeutics, Roche, Novartis, Bluebird Bio and Celgene) and Steering committee for BELIEVE trial (Celgene) and Abfero (safety monitoring committee) SP declares advisory boards for Novartis and Celgene, JP declares advisory board funding for Novartis, Bluebird Bio and Celgene, BK declares advisory board funding for Novartis and Apopharma. The following members of the writing group JM, EA, NS, have no conflicts of interest to declare.

Review process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/guidelines/).

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Audit tool

See separate attachment.

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