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Scottish Paediatric & Adult Haemoglobinopathy Network

Adult Guideline for the use of Iron Chelation in Sickle Cell Disease and Thalassaemia

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NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Introduction

Red cell transfusion has an established role in the management of sickle cell anaemia and thalassaemia. Iron accumulation is an inevitable consequence of chronic blood transfusion – each unit of blood contains approximately 200mg of iron which the patient is unable to excrete. Furthermore, patients with thalassaemia have increased absorption of dietary iron and therefore even those with non-transfusion dependent thalassaemia (NTDT) may develop iron overload. Accumulation of iron in vital organs results in damage which can be life threatening. There is good evidence that the majority of these complications can be prevented if iron stores are maintained within a safe range.

Institution of vigorous iron chelation therapy early in childhood has been responsible for a marked improvement in survival of patients with transfusion-dependent beta thalassaemia. Although iron loading in sickle cell disease is generally much less, in large part due to reduced transfusion, sickle cell disease patients who receive multiple top-up transfusions can require iron chelation therapy. The following recommendations for diagnosis, monitoring and management of iron overload can be applied to patients with predominantly in thalassaemia syndromes but can be used in monitoring sickle cell disease patients.

Aims

- To monitor body iron stores accurately, minimise iron accumulation, and prevent tissue damage and organ dysfunction resulting from transfusion iron overload.
- For patients who are already iron overloaded, to reduce body iron load and minimise the toxic effects of intracellular and extracellular iron.
- To monitor for adverse effects of iron chelator drugs, and to adjust therapy to minimise associated morbidity.

General considerations

Iron chelation is a long term treatment and good patient compliance is crucial to achieve successful outcomes. The decision to commence chelation treatment should be made by a clinician experienced in the use of iron chelators, after counselling patients on the rationale behind treatment, the different chelators available and potential side effects and how the treatment will be monitored.

Indications for assessment of iron loading

Beta thalassaemia major patients on lifelong transfusions Non transfusion dependent thalassaemia patients Homozygous sickle cell patients (occasionally HbSC or S-Beta thalassaemia compound heterozygotes) on regular top-up transfusion

Assessing iron burden

- **Serum ferritin (SF)** – SF levels are an indirect measure of transfusion iron loading but have to be interpreted with caution. Levels are elevated during intercurrent infections, chronic inflammatory conditions and liver disease. They can be used to guide therapy for an individual patient (i.e. going up or down), but do not correlate well at higher levels (e.g.>4000). It is not a tool to be used in isolation when other methods are available.

Of particular note, serum ferritin in NTDT patients, rises much less for the same degree of iron loading (i.e. can be falsely reassuring)

- **Transferrin saturation**: May have a role in assessing mild untreated iron overload, but not when on chelation

- **Liver iron concentration (LIC) by MRI** –
  - R2* MRI - logarithmic assessment between LIC and R2*. (criticism that it is less robust than the Ferriscan method)
  - R2 MRI methodology commercialised by Ferriscan to mgFe/g dw liver measurement and produce a standardised report.

- **Liver biopsy –** A wedge biopsy historically has been used to assess iron, but the reproducibility is poor, particularly if cirrhotic. Its use in current practice is predominantly when the liver is being biopsied for other reasons.

- **Cardiac T2* by MRI:** Reproducible on different scanners using standardised technique. Excellent for measurement of left ventricular ejection fraction (LVEF). LV impairment becomes increasingly likely when T2* falls below 20ms

Table 1: A grading scheme for assessing myocardial iron and guiding changes in chelation therapy:

Risk (if untreated)	T2*
No cardiac iron, low risk of heart failure (HF)	≥ 20 milliseconds
Mild to moderate cardiac iron, low risk of HF	10 – 19 milliseconds
High cardiac iron, moderate risk of HF	6 – 9 milliseconds
High cardiac iron, high risk of HF	< 6 milliseconds

- **Assessment of iron in other organs**: Can be seen in pituitary on MRI but not done routinely. Endocrine assessments should be done as per guidelines

When reviewing an iron loaded patient

Consider

- What is the underlying disease?
- Why is the patient so iron loaded – what is their chelation journey
- Why has there been a change – has their rate of loading changed?
- What has been prescribed and what is being taken?
- Is there dose limiting toxicity
- Are there psychological issues

When to assess iron overload

The risk of iron overload should be considered in all transfusion dependent patients, in patients receiving frequent transfusions, and in patients with significant dyserythropoiesis in the absence of transfusion.

- Once on chelation, the assessment of iron loading should consist of 3 monthly ferritin, annual liver assessment and cardiac assessment depending on previous result (see below)
- For those not on chelation with significant risk e.g. HbE/Beta thal, consider annual MRI liver (ferritin can be monitored but can give false reassurance).

When to start treatment

When the decision to start regular transfusion has been made, then chelator therapy will be required at the point where there is sufficient iron loading to avoid the toxicities of over chelation. In the NTDT is it less clear.

Recommendations include:

- Serum ferritin > 1000mg/L (measured in steady state with normal inflammatory markers on 2 or more occasions > 6 months apart)
- >1000g of red cells transfusions
- R2 Liver MRI – liver Iron > 7mg/g/dw (consider >5mg for NTDT)
- Cardiac T2 MRI <20ms

The 2016 Thalassaemia Standards recommend Tsat >90% and >1000g red cells transfused

Iron chelating drugs

There are three chelating drugs which can be used for treatment of iron overload in TM: desferrioxamine (Desferal®, DFO); deferiprone (Ferriprox®, DFP) and deferasirox (Exjade®, DFX). Current UK licensing indications are presented in table 2.

Table 2: Current UK licensing indications for iron chelating drugs

	DFO (Desferrioxamine)	DFP (Deferiprone)	DFX (Deferasirox)
Children age 2 – 6	First line	Insufficient information	Second line if DFO contra-indicated or inadequate
Children age > 6 and adults	First line	Second line: if DFO not tolerated or ineffective	First line
Route	SC usually given overnight 8-12 hours (can be given iv, see spc for dosing)	Oral, tablet or liquid	Oral, film coated tablet
Dosage	20-60 mg/kg 3-7 times per week (usually 5). Children's dose up to 30 mg/kg	75-100 mg/kg/day (3 divided doses)	7-21 mg/kg/day once daily
t ½	20-30 minutes	3-4 hours	8-16 hours
Excretion	Urinary, faecal	Urinary	Faecal
Contra-indications	Hypersensitivity Should not be used in pregnancy unless risks outweigh benefits	Previous agranulocytosis Pregnancy – contraindicated teratogenic risk	Hypersensitivity Estimated CrCl <60ml/min Pregnancy not known and so not recommended

1. Deferoxamine (DFO, Desferal brand name)

Subcutaneous DFO infusions given 5-6 days per week over 8-12 hours has been a very effective chelation regime for over 30 years. Adherence is the major challenge with DFO.
DFO is administered as a subcutaneous infusion over 10-12 hours (usually overnight), typically 5 nights a week. The frequency and duration of infusions should be tailored to patient's need and adherence, with the aim of using the lowest effective dose. The longer the duration of infusion the better the chelation efficiency, therefore doses should be spread over 5 or 6 days and the dose per day altered, rather than altering the number of days it is administered. For young children, a run in period starting at 2 days /week increasing to 5-6 days is recommended.

Desferrioxamine should be reconstituted with water, and should not be more concentrated than 10% (i.e. 250mg in at least 2.5ml, 1g in at least 10 ml). Disposable elastomeric pre-filled infusers can be used – these are light and noiseless and are prepared in a sterile pharmacy facility, and often delivered to the patient's home.

Subcutaneous insertion – abdominal wall is generally most suitable, and can be divided into 4 quadrants wound umbilicus to allow rotation. Additional sites of thighs and upper arms will be required if >5 x a week.

Local reactions – if local reactions are problematic, consider reviewing technique, altering site, reducing concentration of infusion, or adding a small dose of hydrocortisone to the infusion.

Oral vitamin C has been shown to enhance mobilisation of iron and to increase efficacy of chelation with DFO – therefore it is recommended that children and adults should take ascorbic acid either as a regular daily dose, or prior to each infusion (adults – 200mg, children – 100mg). Ascorbic acid should not be used in the early stages of intensive chelation for patients with cardiac failure or myocardial T2* <10 msec due to the risk of precipitating cardiac toxicity.

Table 3: Suggested ADULT Desferal doses (SPC)

Ferritin	Desferal dose (5 nights)
<2000	25 mg/kg/day
2000-3000	35 mg/kg/day – (SPC dose, likely to need more)
>3000	Up to 60 mg/kg/day

Continuous intravenous DFO (5-6 infusions over 10-12 hours per week using an infusion pump) can be given via a central venous catheter for the following indications:

- Acute or chronic cardiac toxicity due to iron overload
- Early cardiomyopathy detectable by echo or other method
- Poor compliance with SC DFO and inadequate chelation
- Women with ferritin > 2500 who plan a pregnancy

Cardiac rescue for T2* <6ms

Severe cardiac iron loading is associated with significant mortality and requires more aggressive chelation. Below is a recommended regime, but discussion with experienced clinicians is also advised.

Administered via PICC or central line with 24 hour disposable elastomer pre-filled infuser. Anticoagulation with DOAC should be considered to prevent line associated thrombosis. Patient/family will need education around administration of this medication and line care.

1st dose of IV desferal can be established in the outpatient setting if no cardiac issues, with intermittent ECG monitoring and with the patient being observed for signs of allergy.

Starting dose 25mg/kg/day but patient may require higher doses. Doses above 25mg/kg/day are more commonly associated with retinal changes.
Ferritin levels should be monitored at least monthly to guide dose adjustments.

Can be used in combination with Deferiprone for synergistic effect.

Adverse effects:

- Pyrexia
- Swelling/irritation at injection site: add 1-10mg of hydrocortisone to syringe if severe
- Severe allergy is rare but first dose should be given in hospital. Desensitization is usually successful.
- Sudden intravenous boluses can cause nausea, vomiting or hypotension and collapse.
- Deafness (High tone sensorineural loss) is uncommon but can occur with prolonged treatment and higher doses but lower ferritin (increased risk if daily DFO/serum ferritin >0.025). If abnormal audiogram, DFO should be stopped and only reintroduced once audiogram normal with close audiology supervision.
- Visual disturbance – stop immediately if any visual changes reported – commonly deterioration in night vision.
- Growth Retardation in children
- Pulmonary toxicity – acute respiratory distress syndrome has been described following treatment at excessive doses;
- Pregnancy – safety in pregnancy not established therefore DFO should be stopped when pregnant. (Could be considered in certain situations where benefits>risk) Can be given when breast feeding.
- Thrombocytopenia, neutropenia and eosinophilia have all been reported.
- Abnormalities of bone growth such as vertebral dysplasia, pseudo-rickets and genu valgum have been described in pre-pubertal children treated with large doses of DFO.
- Yersinia, mycoplasma, mucormycosis and pneumocystis carinii have been described – stop DFO immediately if any occur.

Therapeutic Index of desferrioxamine

Some of the toxicities of desferrioxamine are associated with over chelation. The therapeutic index is calculated as the mean daily dose in mg/Kg divided by the ferritin level in ug/l.

Eg patient on 45mg/kg 5 nights a week with a ferritin of 2500ug/l has a therapeutic index of

Daily dose is 45 x 5 ÷ 7 divided by 2500 = 0.0128

The therapeutic index should be maintained <0.025 to avoid overchelation.

2. Deferiprone (DFP, Ferriprox brand name)

DFP is orally active but has a relatively short plasma half-life and consequently 3-4 x daily dosing regimes are needed to optimise drug levels. Drug and iron complexes are excreted predominantly in the urine, giving the urine a red colour. Good for cardiac iron, less effective for liver iron.

Dosing and administration:

25 mg/kg body weight, oral use, three times a day for a total daily dose of 75 mg/kg/day. Dosage should be rounded down the nearest half tablet (Ferriprox 500mg tablets). In poor responders, higher doses can be used but dosages above 100 mg/kg/day are not recommended.

Contraindications:

- Hypersensitivity to the active substance or any of the excipients
- History of recurrent episodes of neutropenia
- History of agranulocytosis
- Pregnancy or breast-feeding
- Should not be combined with any other medication known to be associated with neutropenia or which can cause agranulocytosis.

Adverse effects:

- Neutropenia/agranulocytosis (4%/1% cases respectively)
- Red discolouration of urine
- Gastrointestinal side-effects (nausea, vomiting, abdominal pain, increased appetite) are more frequent at the beginning of therapy and usually resolve within a few weeks without treatment interruption.
- Arthropathy (usually reversible and DFP can often be re-introduced)
- Intermittent elevation in ALT
- Zinc deficiency

Management of neutropenia (neutrophil count < 1.5 x 10^9/l):

- Stop Deferiprone
- Repeat full blood count daily until recovery
- After recovery check counts weekly for three more weeks
- If evidence of infection, appropriate investigation and treatment with antibiotics should be instigated
- Consider G-CSF and protective isolation if neutrophil count <0.5 x 10^9/l)
- Re-institute DFP only if absolutely necessary and if there is close monitoring of blood counts. DFP should not be re-instituted if severe neutropenia (neutrophils <0.5 x 10^9/l).

3. Deferasirox (DFX, Exjade)

Deferasirox (Exjade) is a once daily oral iron chelator licensed in the UK for the treatment and prevention of iron overload in both adults and children over 2 years. It was initially made as a dispersible tablet, but is now a film coated tablet with much better GI tolerability.

Dosing and administration

- Starting dose – generally 14mg/kg, but can start 7-21mg/kg/day.
- Maximum dose 28mg/kg/day
- (Availability can be reduced by potent enzyme inducers – review drug interaction)

Exjade should be taken once a day at approximately the same time each day, on an empty stomach or light meal. Should not take with antacids.

Side effects

- GI disturbance (nausea, vomiting, diarrhoea, indigestion, constipation) is common – should be treated symptomatically and ideally treatment not interrupted –much less with FCT than with previous
- Increase in creatinine and transaminases – may be transient, but can limit dose

- Headache
- Abdominal distension
- Proteinuria – monitor whilst on treatment
- Rarer – anxiety, dizziness, early cataract, hearing loss, gastritis, hepatitis, pancreatitis, pigmentation disorder, pyrexia, fatigue, oedema, glycosuria, GI bleeding

4. Combination therapy:

This may need to be considered in patients with severe iron overload where monotherapy is felt to be inadequately reducing iron stores. All combinations have been tried, and are increasing used by experts. The most widely studied has been Desferrioxamine and deferiprone, but all 3 combinations have been studied. Combinations can produce additive or even synergistic iron removal. The recommendation is that if monotherapy is not working, combination therapy should be discussed with an expert.

Monitoring while on therapy

All patients on iron chelation therapy require careful monitoring.

Table 4: Recommendations for toxicity monitoring from individual drug SPCs

	DFO (desferrioxamine)	DFP (deferiprone)	DFX (derferasirox)
Neutrophil count	Not required	Weekly during therapy (and patient letter to present to A&E if unwell with fever)	Not required
Creatinine	Not required	Not required	Twice before start, then weekly during 1st month after initiation and change of dose, thereafter monthly
ALT	Monthly	Monthly	Twice before start, then 2 weekly for first month after initiation of therapy. Thereafter monthly
Urinalysis	Not required	Not required	Twice before start, then weekly during first month after initiation and change of dose. Thereafter monthly
Pure tone audiometry	Annual	6-12 monthly for combination DFO and DFP, not if used as single agent	Annual
Ophthalmology	Annual	Not required	Annual

Monitoring efficacy of treatment and evidence of iron overload

- Serum ferritin should be assessed 3 monthly (decisions should be made on trends over time rather than individual readings)
- Cardiac T2* MRI should be carried out:
    - Every 2 years if the T2* is >20ms and ferritin maintained at <1000 micrograms/L on chelation
    - Every year if T2* is >20ms but ferritin >1000 micrograms/L
    - At least every year if T2* is between 10-20ms
    - 6 monthly if T2* <10ms
    - 3 monthly if T2* <10ms and any evidence of cardiac impairment
- Once yearly Ferriscan of liver
- Review the choice of chelator and doses at 6-12 month intervals.

Adjustment of iron chelation dose

- ***Patients with normal or moderately raised iron stores:***
    - Risk of chelator toxicity increases with ferritin <1000, which LIC <3mg/gdw and DFO:ferritin ratio (therapeutic index)>0.025
    - Serum ferritin consistently <750micrograms/L and no evidence of organ loading, reduce/consider stopping chelation.
    - If reducing desferrioxamine, dose per day should be reduced, not number of days

- ***Patients with acceptable iron stores:***
    - Serum ferritin consistently 750-1500 micrograms/l
    - Liver iron (if available) 3-7mg/g dry weight
    - Cardiac T2* MRI >20 m sec
    - Continue current regimen and offer means to improve ease of treatment (if on Desferrioxamine ensure therapeutic index <0.025)
    - Discussion of alternatives if current regimen not tolerated

- ***Patients with high iron stores:***
    - Serum ferritin consistently > 1500 micrograms/L or increasing trend
    - Liver iron >7 mg/g dry weight- by Ferriscan
    - Cardiac T2* MRI >20 m
    - *All Patients on* Desferrioxamine *or* Deferasirox
        - Optimise dosage and adherence (if on Desferrioxamine ensure therapeutic index <0.025
        - Consider switch to alternative chelator (or combination therapy in thalassaemia patients)
    - *For thalassaemia patients on* Deferiprone *or combined* Deferiprone *and* Desferrioxamine
        - Increase Deferiprone dosage up to 100mg/kg/day and/or increase frequency and dosage of Desferrioxamine, keep therapeutic index <0.025 (combination therapy should be discussed with an expert)

- ***In thalassaemia patients with increased cardiac iron (Cardiac T2* <20 milliseconds) – role of combination therapy should be discussed with an expert. Suggested options***
    - *High body iron stores: Serum ferritin consistently >1500 micrograms/l and/or liver iron >7 mg/g dry weight*

        - Switch to combination Desferrioxamine 40-50mg/kg 2-5 days/week + Deferiprone 75-100mg/kg/day every day
        - Monotherapy with either Desferrioxamine or Deferiprone can be resumed once serum ferritin and liver iron have reduced to levels associated with mild iron loading.
    - *Acceptable body iron stores: Ferritin consistently 500-1500 micrograms/l, and liver iron <7 mg/g dry weight)*
        - Switch to Deferiprone 75-100mg/kg/day seven days per week

Special indications (after expert discussion)

- **Severe myocardial iron loading (Myocardial T2* < 10ms) in a patient clinically in heart failure:**
    - DFO 50-60 mg/kg should be started immediately via a peripheral line and given as a continuous 24hour IV infusion
    - A long-term intravenous line should be inserted to facilitate long-term therapy
    - Simultaneous DFP (75-100 mg/kg/day) should be combined with the DFO infusions as soon as possible

Pregnancy

- Women planning to become pregnant should undergo a thorough assessment of their current transfusion status, cardiac and liver iron loading and chelation regime.
- A risk assessment for maternal health during pregnancy and delivery should be made by the specialist treatment team together with an obstetrician with special interest and previous experience of managing pregnancies in thalassaemia.
- Women who are planning to become pregnant should undergo a period of intensive chelation to reduce SF, LIC and myocardial iron to optimal levels before attempting to become pregnant.
- Oral chelator drugs should be stopped three months before anticipated conception.
- Standard advice for DFO to be withheld throughout pregnancy can be reviewed in cases of high iron loading where the risk of cardiac complications is judged to be high. DFO can be considered in the second and third trimesters. On the basis of current evidence, DFX and DFP should not be used during pregnancy.

Renal impairment

- DFX should not be used if creatinine clearance < 60 ml/min but can be considered in patients with end stage kidney disease on renal replacement therapy. Low dose desferrioxamine given during the last hour of dialysis is an alternative.
- DFO or DFP can be used in patients with renal impairment (creatinine clearance < 60ml/min) but chelator doses should be kept as low as possible, and monitoring for toxicity should be intensified, with clinical, haematological and biochemical assessment every month, and audiology and ophthalmology checks every 3-6 months.

Adapted from:

Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. 3rd addition, 2016

Summary Product Characteristics – Desferrioxamine, Deferiprone and Deferisirox

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