**Iron overload in patients with Thalassaemia**

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| **Profile** |
| **Version:** | *V3.1* |
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| **Executive/Divisional sponsor:** | *Dr Lisa Pickering, Divisional Chair* |
| **Applies to:** | *All staff involved in the care of patients with Sickle Cell Disease* |
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| **Approval** |
| **Approval person/Committee:** | *MedCard Divisional Governance Board* |
| **Date:** | *14th February 2019* |
| **Approval person/Committee:** | *Hospital Transfusion Committee* |
| **Date:** | *March 2020* |

# Contents

|  |  |
| --- | --- |
| **Paragraph** | **Page** |
|  | Executive Summary |  |
|  | Policy Gateway |  |
| 1 | Introduction |  |
| 2 | Purpose |  |
| 3 | Definitions |  |
| 4 | Scope |  |
| 5 | Roles and responsibilities |  |
| 6 | Other headings as appropriate |  |
| 7 | Implementation and dissemination |  |
| 8 | Monitoring compliance |  |
| 9 | Associated documents |  |
| 10 | References |  |

**Policy Gateway**

Please complete the checklist and tables below to provide assurance around the policy review process.

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| ☒ I have involved everyone who should be consulted about this policy/guidance☒ I have identified the target audience for this policy/guidance ☒ I have completed the correct template fully and properly☒ I have identified the correct approval route for this policy/guidance ☒ I have saved a word version of this policy/guidance for future reviews and reference  |

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| Please set out what makes you an appropriate person to conduct this review: |
| Consultant for Adult Haemoglobinopathy service |

|  |
| --- |
| Please set out the legislation, guidance and best practice you consulted for this review: |
| * West Midlands Review Service – Quality Standards: Health Services for People with Haemoglobin Disorders (2018/19)
* Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018 (Sickle Cell Society) <https://www.sicklecellsociety.org/wp-content/uploads/2018/04/Web-version-FINAL-SCS-Standards-GSM-6.4.18.pdf>
* British Society Haematology : guidelines Red Cell Transfusion in Sickle Cell Disease Part I and Part II (7.11.17 and 18.11.18) <https://b-s-h.org.uk/guidelines/guidelines/red-cell-transfusion-in-sickle-cell-disease-part-l/>
* Clinical Commissioning Policy: Treatment of iron overload for transfused and non transfused patients with chronic inherited anaemias. Ref :NHS England 16070/P (April 2016)
 |

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| Please identify the key people you involved in reviewing this policy why, and when: |
| * Kelly Feane, Lead Transfusion Practitioner
* Jan Chase, lead pharmacist – Cancer services
* Dr Lisa Anderson, Consultant Cardiologist
 |

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| Summarise the key changes you have made and why: |
| Updates in line with the UK standards of care for SCD Updated contact detailsV3.1 – formatting update |

**Executive Summary**

Transfusion in patients with Sickle Cell Disease (SCD) and thalassaemia is increasing rapidly across the UK but with variability in indications and lack of robust evidence in many cases. This guideline covers the managements of the consequences of transfusion – predominantly iron overload and the need for iron chelation.

## Introduction

Transfusion in patients with Sickle Cell Disease (SCD) and thalassaemia is increasing rapidly across the UK but with variability in indications and lack of robust evidence in many cases. This guideline covers the managements of the consequences of transfusion – predominantly iron overload and the need for iron chelation.

These guidelines should be used in conjunction with the St George’s University Hospitals NHS Blood Transfusion Policy <http://stg1wordpress01/wordpress/wp-content/uploads/2016/06/Blood-Transfusion-Adults.pdf>

## *Status and Purpose*

*This document is part of the Haematology Department’s guidelines on the management of patients with SCD and is applicable to all staff involved in the care of these patients.*

## *Definitions*

*Sickle Cell Disease – inherited lifelong condition due to abnormal haemoglobin variant.*

## *Scope*

*This guideline is relevant to the care of patients with SCD requiring elective and emergency surgery at St.George’s.*

## *Roles and Responsibilities*

### *5.1 Haemoglobinopathy team (Consultant haematologists, Clinical Nurse Specialist and Clinical Health Psychologist) – Responsible for the care of these patients, developing and updating guidelines to be reflective of good practice and to deliver the training to ensure good safe care.*

***5.2 Medical staff involved in the care of patients with SCD.*** *Responsible with the oversight of the haemoglobinopathy team to deliver the care to these patients in line with guidelines where possible.*

***5.3 Nursing staff and allied health professionals involved in the care of patients with SCD on wards, day unit and other areas of St George’s*** *responsible with the oversight of the haemoglobinopathy team to deliver the care of these patients in line with guidelines where possible.*

1. **Content**

**Iron Monitoring and Treatment in Patients with Thalassaemia**

**MONITORING**

All patients with Transfusion Dependent Thalassaemia (TDT) will be receiving chelation by adulthood having started treatment in early childhood. Iron levels need to be monitored in these patients in order to guage the efficiency of their chelation regimen, ensure timely changes are made as needed and to assess compliance.

Other patients with haemoglobinopathies should have regular monitoring of ferritin levels: if the patient is **not** on a regular transfusion programme then this is done as part of the annual review. If the patient **does** receive regular transfusions then ferritins should be measured at each transfusion and reviewed at day unit meetings and with the patient in clinic.

Imaging in patients on a transfusion programme: T2\* MRI scans to assess liver and cardiac iron loads at St George’s Hospital – can be requested via iClip and are performed by the MRI scanner in neuroradiology, Atkinson Morley Wing.

|  |  |
| --- | --- |
| No cardiac or liver iron. Stable or falling ferritin | Scan every1- 2 years |
| No cardiac or liver iron. Rising ferritin | Scan annually until stable |
| No cardiac iron. Moderate liver iron | Scan annually (or more frequently if indicated) |
| Cardiac involvement | Scan annually (or more frequently if indicated) |
| Moderate to severe cardiac iron, poor compliance, rising ferritin | May need scan at 6 months |

Chelation should be considered when more than 20 units of blood have been transfused, the serum ferritin is over 1000 or there is radiological evidence of iron overload.

**Patients with TDT** will have annual cardiac reviews (in the joint cardiac – thalassaemia annual clinic), will receive echocardiograms and cardiac MRIs as indicated and endocrine reviews (with pituitary screening and glucose tolerance tests)

**Patients with non-transfusion associated iron overload (eg Non Transfusion Dependent Thalassaemia, NTDT)**

These patients are at risk of non-transfusion associated iron overload due to ineffective erythropoiesis.

Patients with NTDT are reviewed at least annually and not only should they be monitored for iron overload but they should be made aware of the possibility and need for chelation despite infrequent transfusions.

Monitoring should be via serum ferritin and as above if Ferritin >800 then MRI imaging should be undertaken

Imaging schedule should then follow as above

Chelation decisions as per those with TDT – see next section

Patients with NTDT should be offered annual review in the cardiac-thalassaemia annual clinic.

St George’s Healthcare NHS trust has a very small cohort of patients with thalassaemia intermedia and so referral to the quaternary service at the Whittington Hospital should be considered for review, joint management or advice where necessary or discussion of clinical trials.

**TREATMENT OF TRANSFUSION RELATED IRON OVERLOAD**

Treatment Options for Adult patients

**First line therapy**

* deferasirox (Exjade, film coated tablets) 14-28 mg/kg/day as a once daily dose.
* desferrioxamine (Desferal,) 40mg/kg/day minimum 5 days a week as 8-12h sc infusions
	+ In adults the desferrioxamine dose can be increased to 40-60mg/kg/day as 8 to 24 hour infusions sc depending in the severity of iron overload and patients ability to comply.

**Second line therapy options**

In patients unable to tolerate desferrioxamine or deferasirox mono-therapy, or where control of iron load is not adequate there are the following options

* deferiprone mono-therapy (75-100mg/kg/day in three divided doses) with careful monitoring of hepatic iron
* Deferiprone and desferrioxamine (various regimens).

**Patients with cardiac iron overload (T2\* >8ms, and patient asymptomatic)**

For patients with evidence of increased myocardial iron loading, irrespective of the level of serum ferritin or liver iron, intensification of therapy should be considered. (including achieving a realistic account of how much chelation is currently being taken)

* Add deferiprone to desferrioxamine therapy.
	+ The optimal regimens will depend on individual patient: their age, their ability to comply with each chelation modality and the history of previous chelation therapy.
* Intensification of desferrioxamine dose and or frequency and /or switching from SC to IV
* Increasing dose of deferasirox FCT (21-28mg/kg/day)
* switch to deferiprone monotherapy, particularly if liver iron is well controlled

Other combination therapies will need to be discussed and agreed at specialty MDT and with pharmacy.

**T2\* values <8ms and normal heart function**,

* desferrioxamine and deferiprone (exact regimen requires careful consideration)

Other combination therapies will need to be discussed and agreed at specialty MDT and with pharmacy.

These patients must be discussed and referred to Dr Lisa Anderson for review and where appropriate at the regional specialty MDT

**Ventricular dysfunction**

myocardial iron loading (T2\*<20ms) with reduced LVEF

* Consider 24h desferrioxamine continuous infusion preferably intravenously
* Intensive combination regime of desferrioxamine with oral deferiprone

Other combination therapies will need to be discussed and agreed at specialty MDT and with pharmacy

These patients must be discussed and referred to Dr Lisa Anderson for review and where appropriate at the regional specialty MDT

**Patients with clinical heart failure:**

* Admit for intensive 24h IV desferrioxamine with or without deferiprone and cardiology review
* On discharge from hospital continue on monotherapy with continuous intravenous desferrioxamine or combination therapy with desferrioxamine and deferiprone orally
* Follow up also with Dr Lisa Anderson

**Ophthalmological Review when on Iron Chelation**

Desferrioxamine

Asymptomatic patients when starting desferrioxamine should have a baseline review including electrophysiology and retinal imaging prefably within 6 weeks of starting. They will also be seen in the medical retina clinic after the EDD for documentation of any retinopathy.

These patients should have yearly electrophysiology and psychophysic investigations

Symptomatic patients should be discussed with ophthalmology urgently as desferrioxamine can be retinotoxic. Symptoms are usually after a spell of high dose intravenous therapy. They will require urgent electrophysiology and psychophysic investigations with a full ophthalmological assessment for any abnormalities found.

Deferasirox and Deferiprone

There is less clear evidence of any retinotoxicity and so these patients should be monitored clinically and discussed with ophthalmology if there are concerns of any symptoms.

All patients will be offered review at annual sickle eye clinic with documentation of their chelation drugs.

**Audiological Review when on Iron chelation**

Desferrioxamine

Asymptomatic patients when starting desferrioxamine should have a baseline audiology review either before or within 6 weeks of starting.

Symptomatic patients should be discussed with audiology urgently

Deferasirox and Deferiprone

There is less clear evidence of any ototoxicity but currently we recommend annual audiological review

**Medications**

*All doses and dose adjustments should be confirmed with up to date product literature and the British National Formulary. They should also be discussed with the haematology consultant managing that patient.*

***Deferasirox (Exjade)***

Deferasirox is an oral iron chelator licensed in sickle cell and thalassaemia patients with iron overload.

Prescriptions for deferasirox should only be initiated after consultation with haematology consultant. Deferasirox is a hospital only prescription. It is indicated for the treatment of chronic iron overload in patients with BTM who are older than 6yrs

*Dose*

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Film-coated tablets/granules**  | **Transfusions**  | **Serum ferritin**  |
| **Starting dose**  | **14 mg/kg/day**  | After 20 units (about 100 ml/kg) of PRBC | >1,000 µg/l |
| **Alternative starting doses**  | 21 mg/kg/day | >14 ml/kg/month of PRBC (approx. >4 units/month for an adult) |  |
|  | 7 mg/kg/day | <7 ml/kg/month of PRBC (approx. <2 units/month for an adult) |  |
| For patients well managed on deferoxamine | One third of deferoxamine dose |  |  |
| **Monitoring**  |  |  | **Monthly**  |
| **Target range**  |  |  | **500-1,000 µg/**l |

*Dose alterations due to response*

|  |  |  |  |
| --- | --- | --- | --- |
| **Adjustment steps** (every 3-6 months) | **Increase**  |  |  |
| 3.5 - 7 mg/kg/dayUp to 28 mg/kg/day |  | >2,500 µg/l |
| **Decrease**  |  |  |
| 3.5 - 7 mg/kg/day |  | <2,500 µg/l |
| In patients treated with doses >21 mg/kg/day |  |  |
| - When target is reached |  | 500-1,000 µg/l |
| **Maximum dose**  | **28 mg/kg/day**  |  |  |
| **Consider interruption**  |  |  | **<500 µg/l**  |

*Dose alterations due to renal impairment*

* See current SPC

*Dose alterations due to hepatic impairment*

* Interrupt treatment if persistent or progressive increase in liver enzymes.

*Contraindications*

Deferasirox should not be used in combination with other chelators

It is contraindicated in patients with a creatinine clearance <60ml/min

*Monitoring / Tests*

* Prior to initiating treatment, the patient requires serum ferritin, renal and liver biochemistry. Audiology and ophthalmology review
* In first month, renal and liver biochemistry every 2 weeks
* Every 4-8 weeks, ferritin, renal and liver biochemistry
* Urine dip for protein assessment

***Desferrioxamine (Desferal)***

*Dose*

• 20–50 mg/ kg as a subcutaneous infusion over 8-12 hours on 3-7 days each week

• Consider oral vitamin C (200mg oral ascorbic acid) to be taken separately to food to enhance chelation

*Monitoring*

• Annual ophthalmology and audiology review including baseline

• Monitor ferritin and MRI scan to ensure response

**NB**

Desferrioxamine must be stopped and patients admitted for treatment and investigation if they develop abdominal pain and diarrhoea. *Yersinia* infection must be excluded.

Desferal can be supplied as a preprepared ‘bubble’ for self-administration at home. It will need to be collected from Haematology day unit every 2 weeks. Patients and or carers can be trained on day unit to be self-sufficient at using their desferrioxamine.

Desferrioxamine can be administered intravenously (iv) or for continuous infusions rather than just 12 hours depending on iron load and individual patient circumstances

In cases of cardiac iron overload it can be used in combination with deferiprone. This must only be initiated via the haematology consultant

***Deferiprone (Ferriprox)***

Deferiprone is an oral chelation agent which may be used in dual therapy with deferasirox in patients where optimum chelation is not being achieved. It can also be used as a single agent in patients who cannot tolerate desferrioxamine or deferasirox.

On initiation, regular FBC should be monitored weekly as there is a risk of drug induced neutropenia (agranulocytosis) with this medication.

Doses usually start around 25mg/kg *tds* (75mg/kg) and do not exceed 100 mg/ kg / day

##  Dissemination and implementation

### 7.1 Dissemination:

Guidelines will be available on the departmental intranet page and available in paper form in the junior doctor office in haematology.

### 7.2. Implementation

Guidelines will be promoted by the haemoglobinopathy team.

## Consequences of Breaching the Policy

## Failing to follow this policy could lead to action under the Trust’s disciplinary policy.

## Monitoring compliance

The table below outlines the process for monitoring compliance with this document.

|  |
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| **Monitoring compliance and effectiveness table** |
| **Element/ Activity being monitored** | **Lead/role** | **Methodology to be used for monitoring** | **Frequency of monitoring and Reporting arrangements** | **Acting on recommendations and Leads** | **Change in practice and lessons to be shared** |
| *WMQRS peer review quality standards* | *Consultant haematologist* | *As required (every 2-3 year)* | *The lead or committee is expected to read and**interrogate the report to**identify deficiencies in the system and act upon them. Consider stating this responsibility in committee terms of reference.* | *Required actions will be identified and completed in a specified timeframe.**Consider stating this responsibility in committee terms of reference.**These will be discussed at Divisional governance board* | *Required changes to practice will be identified and actioned within a specific timeframe. A lead member of the team will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders.* |

## Associated documentation

Incentive Spirometry guideline for adults admitted with sickle cell crisis at risk of acute chest syndrome

## References

* West Midlands Review Service – Quality Standards: Health Services for People with Haemoglobin Disorders (2018/19)
* Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018 (Sickle Cell Society) <https://www.sicklecellsociety.org/wp-content/uploads/2018/04/Web-version-FINAL-SCS-Standards-GSM-6.4.18.pdf>
* British Society Haematology : guidelines Red Cell Transfusion in Sickle Cell Disease Part I and Part II (7.11.17 and 18.11.18) <https://b-s-h.org.uk/guidelines/guidelines/red-cell-transfusion-in-sickle-cell-disease-part-l/>