**Management of iron overload in patients with Sickle Cell Disease**

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| **Profile** | |
| **Version:** | *V3.1* |
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| **Executive/Divisional sponsor:** | *Dr Lisa Pickering, Divisional Chair (v3.0 February 2019)* |
| **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* |

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**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/> * Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease NICE Medical technologies guidance [MTG28] (2016) |

|  |
| --- |
| Please identify the key people you involved in reviewing this policy why, and when: |
| * Jan Chase – lead pharmacist, Cancer Services * Kelly Feane – lead transfusion practitioner * Dr Lisa Anderson – Consultant Cardiologist |

|  |
| --- |
| Summarise the key changes you have made and why: |
| Updates in line with the UK standards of care for SCD  Updated contact details  V3.1 formatting updates |

**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. Guidance is now issued by both the British Standards of Haematology (2016) and from the Standards of Clinical Care for adult patients with SCD in the UK. A consequence of blood transfusion therapy is iron overload and these guidelines describe the management of prevention and treatment of iron overload and the use of 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. Guidance is now issued by both the British Standards of Haematology (2016) and from the Standards of Clinical Care for adult patients with SCD in the UK. These guidelines describe the indications, management and process (including safety and selection) for blood transfusion in SCD and thalassaemia. The guideline also covers 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 SCD**

Blood transfusion in sickle cell disease has been shown to lead to iron deposition within the liver predominantly (and therefore is associated with liver damage, fibrosis, cirrhosis and possible liver failure) but also extra hepatic organs. There is less robust evidence regarding chelation in sickle cell disease compared to thalassaemia but the aim of chelation is to reduce the risk of complications of iron overload, which may develop with intermittent or regular transfusions

Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018 (Sickle Cell Society) have the following standards

* All patients with a raised serum ferritin persistently ( >1000 μg/l ) who have been previously transfused should have quantitative monitoring of liver iron concentration using magnetic resonance imaging (MRI).
* Iron chelation is recommended in patients who have a liver iron concentration of >7mg/g dry weight on MRI scanning.
* Patients receiving long term blood transfusion should have regular monitoring for iron overload and appropriate iron chelation therapy according to their iron burden.
* All patients receiving iron chelation therapy should be regularly monitored for therapeutic effect and chelator toxicity.
* Support should be provided to patients to help improve adherence to chelation therapy.

At St George’s T2\* MRI scans are used to assess both 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.

Iron chelation strategies will depend on patient type, transfusion history and other comorbidities.

**Patients receiving / received intermittent or occasional simple transfusions**

* These patients can accumulate considerable amounts of iron over year .
* Ferritin should be assessed regularly, at least at annual review
* MRI monitoring undertaken if the ferritin is persistently >1000μg/l.
* Iron chelation should be offered to all patients with liver iron values above 7mg/g/dw and considered for those with liver iron concentration of 5-7mg/g/dw dependant on co-existing morbidity in the heart or liver.

**Patients on regular top up transfusion programme**

* These patients should be offered iron chelation therapy once 10-20 units of blood have been administered or the ferritin is above 1000μg/l.
* Iron chelation should be continued for as long as the patient remains on transfusions with the aim to keep liver iron <5mg/g/dw and cardiac T2\*>20ms.

**Patients on automated regular exchange transfusions**

* Many patients on long-term transfusion therapy will receive automated exchange transfusions.These are less likely to cause iron loading than long term simple transfusion and are recommended by the National Institute of Health and Clinical Excellence (NICE).
* Some patients may still load iron, particularly if the post-exchange haemoglobin is higher than that pre-exchange. MRI scanning is indicated if there is a raised or increasing ferritin level (>1000 μg/l).
* Patients who are iron loaded (LIC >7mg/g) when they embark on long-term automated transfusion therapy should be treated with iron chelation therapy and be monitored for iron overload with serial serum ferritin and MRI LIC.
* Iron chelation can be stopped once the ferritin is <500μg/l or liver iron <5mg/g/dw.
* All patients who are loading iron on the automated exchange transfusion programme are discussed in apheresis MDT where timings, indications and technicalities of their procedures are reviewed to see if patients may benefit from stopping transfusions, changing in frequency, other disease modifying interventions or any other options.
* Where possible patients who are iron loaded or iron neutral (and not iron deficient) should be offered hypovolaemic depletion on the apheresis machine.
* Ferritins, Pre and Post Hcts, S% are all reviewed regularly at apheresis clinical MDT.

**Imaging Schedule**

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

**Patients with SCD** should be referred for a cardiology opinion (Dr Lisa Anderson) if there are concerns regarding cardiorespiratory symptoms, abnormal echocardiograms and abnormal MRI scans demonstrating cardiac iron overload. They should also be referred to the endocrinology team if there are concerns regarding pituitary or hormonal disturbance which may be due to iron overload

**TREATMENT OF TRANSFUSION RELATED IRON OVERLOAD**

*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 and desferrioxamine are both licensed as iron chelators in SCD and lead to similar

dose-dependent liver iron concentration (LIC) reductions in transfused SCD patients

Deferiprone is not licensed for SCD but there is evidence that it is as effective as

desferrioxamine.

***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 and in patients with sickle cell anaemia with chronic iron overload in whom

desferrioxamine is contraindicated or considered inadequate.

*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/day  Up 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 unless discussed at specialist centre MDT and with pharmacy department

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)***

Desferrioxamine is the first line chelator in patients with sickle cell anaemia and chronic iron overload secondary to repeated blood transfusions.

*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 desferrioxamine

in patients where optimum chelation is not being achieved – usually in patients with significant iron overload and it is thought to have a particular benefit in those with cardiac iron overload. Combination therapy should only be instigated after

discussion with a specialist centre.

It is not licensed for use in SCD and patients should be made aware of this and the reasons for its use should be clearly documented in the notes. Adverse effects include agranulocytosis, neutropenia and

arthropathy, as well as gastro-intestinal disturbance, intermittent elevation in alanine

transaminase (ALT) and zinc deficiency.

Agranulocytosis (neutrophil count < 0.5 × 109/l) has been described in up to 1.5% of patients, at a median of 162 days after starting treatment, and is the most severe side effect of this drug. Weekly full blood count monitoring is recommended whilst on this treatment.

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

**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

## 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.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **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/>