**Guidelines for the management of hyperhaemolysis in patients with Haemoglobinopathies, including the use of intravenous immunoglobulin (IVIg)**

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| **Profile** | |
| **Version:** | *V3.0* |
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| **Executive/Divisional sponsor:** | *Via Hospital Transfusion Committee* |
| **Applies to:** | *All staff involved in the care of patients with Sickle Cell Disease* |
| **Date issued:** | *V3.0 February 2020* |
| **Review date:** | *February 2023* |
| **Approval** | |
| **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/> |

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| Please identify the key people you involved in reviewing this policy why, and when: |
| * Kelly Feane – Lead Transfusion Practitioner * Dr Elizabeth Rhodes –consultant Haematologist |

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| Summarise the key changes you have made and why: |
| New Guideline |

**Executive Summary**

Hyperhaemolysis is a well-recognized but rare complication of blood transfusion in patients with Haemoglobinopathies (Sickle Cell Disease and Thalassaemia).

It is characterised by rapid haemolysis following a blood transfusion, and the post-transfusion haemoglobin (Hb) will often be lower than the pre-transfusion Hb, implying the destruction of recipient as well as donor red blood cells (RBCs).

This Guideline describes the management of this complication, including the use of immunoglobulin which is a blue indication according to the Department of Health Clinical Guidelines for Immunoglobulin Use.

**1.0 Introduction**

Hyperhaemolysis is a well-recognized but rare complication of blood transfusion in patients with Haemoglobinopathies (Sickle Cell Disease and Thalassaemia).

It is characterised by rapid haemolysis following a blood transfusion, and the post-transfusion haemoglobin (Hb) will often be lower than the pre-transfusion Hb, implying the destruction of recipient as well as donor red blood cells (RBCs).

This Guideline describes the management of this complication, including the use of immunoglobulin which is a blue indication according to the Department of Health Clinical Guidelines for Immunoglobulin Use.

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. **Contents** 
   1. Background
   2. Patient Groups
   3. Diagnosis
   4. Investigations
   5. Treatment
   6. Dosage
   7. Monitoring of Treatment
   8. Monitoring of Guideline

**Background**

Blood transfusion is an important treatment in the management of patients with sickle cell disease (SCD) and other haemoglobinopathies, however, about one third of transfused SCD patients develop antibodies to red antigens, becoming allo-immunised, and around 10% develop the most serious consequence of this allo-immunisation which is a delayed haemolytic transfusion reaction (DHTR).

In many Haemoglobinopathy patients presenting with DHTR, the patient’s ***haemoglobin level falls below*** the pre-transfusion level suggesting destruction of transfused RBCs as well as the patient’s own RBCs. This is referred to as hyperhaemolysis.

It is characterised by rapid haemolysis and may be associated with fever and with pain typical of sickle cell disease. The direct antiglobulin test (DAT) may be either negative or positive and new red cell allo-antibodies are not usually identified but may be present. There may be a reticulocytopenia.

Hyperhaemolysis can recur in such patients following blood transfusions several months or years after the initial episode.

Patients with hyperhaemolysis should be treated with intravenous immunoglobulin (IVIg) and IV Methylprednisolone. Additional transfusion has been associated with increasing haemolysis and worsening anaemia, and should be avoided if possible. However, in cases where there is very rapid haemolysis and critical anaemia, transfusion is required and should be preceded with IVIg.

Erythropoietin, iron replacement, B12 and folate replacement is usually required and should be considered.

Hyperhaemolysis can recur many years after the first episode and transfusion is generally avoided if possible in all patients who have had an episode. However, should a blood transfusion be clinically indicated in such a patient, this must be discussed and agreed with a haematology consultant, and the patients should be retreated with IVIg prior to transfusion.

**Patient Groups**

1) IVIg and IV Methylprednisolone should be considered in patients with SCD who present with evidence of severe haemolysis following a blood transfusion.

2) Patients with SCD and hyperhaemolysis who continue to haemolyse despite initial treatment and have worsening anaemia may need a further transfusion. This should be preceded by IVIg and discussion with the haematology consultant covering SCD.

3) Patients with SCD and a history of hyperhaemolysis are at risk of recurrence. If transfusion is necessary it should be preceded by IVIg.

**Diagnosis**

Hyperhaemolysis should be considered in any patient with haemoglobinopathy who presents with increasing haemolysis after a blood transfusion, typically, 1 week post transfusion, but may occur sooner than this if the patient is re-challenged with transfusion.

Clinical features: Increasing jaundice, dark urine (‘coca-cola’ coloured), anaemia. They may also have a fever, back, leg or abdominal pain, hepatomegaly or hepatic discomfort.

**Investigations:**

* ***FBC***: Worsening anaemia – Hb may fall to below the pre-transfusion level.
* ***Reticulocytes:*** May be raised (in keeping with haemolysis) or decreased, due to suppression of red cell production.
* ***Direct Antiglobulin Test (DAT):*** Usually negative but can be positive, transfusion laboratory should send for an eluate if DAT is positive.
* ***Group and screen:*** New allo-antibodies may be found but are usually absent.
* **Haemoglobin electrophoresis to measure HbS% and HbA%:** this is useful to quantify how much, if any, HbA (transfused blood) remains.
* ***Other markers of haemolysis***:
  + Raised Bilirubin
  + Raised LDH
  + Hyperferritinaemia may also be seen as a marker of macrophage activation

**Treatment**

* All haemoglobinopathy patients with suspected hyperhaemolysis must be discussed with a Sickle (red cell) Consultant during normal working hours or the on-call Haematology Consultant covering non-malignant haematology if out-of-hours.
* Supportive management should continue with analgesia, hydration and oxygen therapy as required.
  + Prescribe folic acid 5mg.
  + Consider treatment with erythropoietin and providing IV iron replacement if not iron replete (i.e. if ferritin <100ng/ml).
  + Consider B12 replacement.
* Primary treatment is with IV Methylprednisolone and IVIg.
* Blood transfusion may be necessary if clinically indicated (profound symptomatic anaemia), but should only be given after discussion with the Haematology Consultant.
* Phenotyped blood should be given (CDE and Kell matched).

* When a case of hyperhaemolysis is suspected, and having discussed with the Haematology Consultant, it is important to communicate the suspected diagnosis to the transfusion biomedical scientist who will add a comment to the patient record.

**Dosage**

* **Intravenous immunoglobulin (IVIg)**

Adult and paediatric dose (unlicensed indication): 1g/kg once daily for 2 days (total dose = 2g/kg).

Administration and the choice of preparation is according to individual Trust guidance. Round the dose to nearest vial size (5g, 10g and 20g vials available).

IVIg use for this indication has been approved by the Immunoglobulin Assessment Panel 30th November 2010. The Department of Health immunoglobulin guidelines have changed this indication from grey to blue. At St George’s IVIg is prescribed on specific request form and please contact pharmacy to expedite issue

* **Methylprednisolone**

Adults: 500mg IV for 2 days

Paediatrics 10mg/kg IV for 2 days (maximum dose 500mg)

Review dose after 2 days.

* **Erythropoietin**

NeoRecormon 300iu/kg once daily for 5 days.

Then 300iu/kg once daily on alternate days (i.e. 3 times per week).

Hyperhaemolysis can be severe and there are documented cases that have had fatal outcomes. If there is ongoing haemolysis despite actions above this must be discussed urgently with the haematology consultant for SCD. There are case reports of successful outcomes using eciluzimab and rituximab which are not licensed nor routinely funded currently but may need to be considered.

**Monitoring of treatment**

* Haemoglobin: Target is return of haemoglobin to baseline.
* Stop erythropoietin if the haemoglobin returns to baseline, or if lack of response after full treatment dose.

**Monitoring of this Guideline**

* Use of IVIg for this indication will be monitored via the DH Immunoglobulin Demand Management Programme Database.

## 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/>

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Win N, New H, Lee E, De La Fuente J. Hyperhemolysis syndrome in sickle cell disease: case report (recurrent episode) and literature review. (2008) Transfusion. 48; 1231-1238

Yazdanbakhsh K, Ware R, Noizat-Pirenne F. Red blood cell alloimunization in sickle cell disease : pathophysiology, risk factors and transfusion management. (2012) Blood. 120; 528-537