1. Introduction and Who Guideline applies to

This document aims to offer clinical guidance in association with transfusion practices in relation to sickle cell patients. Further guidance on transfusion can also be found in the trust wide transfusion policy document.

The policy applies to all staff responsible for patients with sickle cell disease.

2. Guideline Standards and Procedures

General Principles:

1. In line with the British Society of Haematology (BSH) guidelines published in 2016, the goals of red cell transfusion in patients with sickle cell disease are to:
    a. Improve the oxygen carrying capacity by correcting anaemia
    b. Preventing or reversing complications of sickle cell disease related to vaso-occlusion and haemolysis
2. Patients with sickle cell disease are at increased risk of complications related to red cell transfusion and so any decision to transfuse must be made in conjunction with a haematology specialist.
3. **All** new patients should have a transfusion history taken and extended red cell phenotyping performed in addition to a baseline group and antibody screen (or genotyping if recently transfused)
4. Blood bank **must** be informed that the patient has a diagnosis of sickle cell disease and requires sickle negative blood. The clinical team should also make blood bank aware if there is any clinical information available that may impact blood provision, including their usual treating hospital if not known to UHL previously. Where possible, Blood bank should interrogate LIMS and SPICE to look for any known transfusion issues.
5. If a transfusion is required, sickle negative, ABO compatible, Rh and Kell matched blood should be given. If possible, blood should be <10 days old for a top up transfusion and <7 days old for an exchange transfusion. Blood should also be CMV negative in pregnant patients.
6. Patients with complex transfusion needs should have an agreed plan in the event of elective or emergency transfusion.

Investigations

For all transfusions in patients with sickle cell disease it is important to record the following information before and after the procedure:

- Hb
- Reticulocytes
- WCC
- Platelets
- HCT
- Sickle %
- U&E
- Bone profile
- LFTs

Types of transfusion and indications

The following types of transfusion can be given to patients with sickle cell disease:

1. Top up transfusion
2. Exchange transfusion
    a. Manual
    b. Automated

The BSH indications for transfusion are included in Appendix 1.

Top up transfusion

An acute drop in haemoglobin >20g/l from baseline should prompt a review to assess for the cause of anaemia and the possible need for a red cell transfusion.

Please note, transfusion will not reduce the severity or duration of an uncomplicated painful crisis.

An acute drop in haemoglobin may occur due to the following reasons:

- Splenic or hepatic sequestration
- Acute chest syndrome
- Mesenteric syndrome
- Aplastic crisis
- Blood loss
- Haemolytic crisis

Top up transfusions can also be considered for pre-operative management or for management of pregnancy in sickle cell disease.

In general, the aim should be to return the patients Hb to their baseline to avoid risks relating to hyperviscosity.

The minimum amount of blood necessary should be transfused.

The volume of packed red cells required in mls can be calculated by:

(desired Hb-Current Hb) x patients weight x K (0.4)

Exchange Transfusion

This procedure involves removing the patient's own blood (containing sickle cells) and replacing it with donor blood which is sickle cell negative. This is required for:

1. Emergency management of acute sickle complications, such as:
    a. Acute chest syndrome
    b. Acute stroke
    c. Fulminant hepatic failure
    d. Splenic or hepatic sequestration
    e. Priaprism unresponsive to therapy
    f. Clinical deterioration in pregnancy*

2. Outpatient management prior to elective procedures
    a. Pre-operative
    b. Pre-flying

***All** pregnant women with sickle cell disease should be seen in the joint obstetric/haematology clinic. Pregnant women admitted with sickle cell disease should be discussed with the obstetrician and haematologist on call. Additional foetal monitoring may be required.

Manual exchange

This method is time consuming and it may not be possible to achieve the desired reduction in HbS% in one procedure. This is usually an emergency procedure and an automated exchange should be performed at the earliest opportunity following this.

Practical points

The manual exchange procedure should be performed by a member of the haematology team after discussion with the on call haematologist.

Close observation and monitoring of vital signs is compulsory. Admission to a high dependency unit is preferred but not essential providing that adequate care of an acutely unwell patient can be maintained.

UHL policy with regards to monitoring and checking procedures should be followed throughout.

6-8 units of cross matched blood are usually required. A pre- and post-procedure FBC and HbS% are necessary to assess efficacy and reduce complication risk. The post-Hb should not exceed 10g/dl if Hb S% is more than 30%. Haematocrit should not exceed 0.33.

The procedure is outlined in Appendix 2 (adapted from STSTN network guideline)

Automated exchange

When possible, this method is preferred to manual exchange as it is quicker and allows greater control of the circulating volume. Access to automated exchange will depend on the time of day and the availability of trained staff to operate the cell separator machine. This decision should be made by a consultant haematologist in liaison with the on call apheresis nurse (available on medirota).

If a decision to perform automated exchange is made, the SOP OHQS-W-34 should be followed.

Practical points

Good venous access is essential to maintain adequate flow rates, which are necessary to keep the machine running. Temporary central venous lines may be necessary in some patients.

Prior to an automated exchange, the following information is required:

- Patients details
    - Height
    - Weight
    - Haematocrit
- Haematocrit of transfused blood (0.6 for SAG-M blood)
- Desired post Hct
    - Usually 0.35 to avoid hyperviscosity
- Desired % fraction of cells remaining (FCR)
    - 20%
- Fluid balance
    - Aim for neutral balance

During an exchange, the patient may experience symptoms related to hypocalcaemia. If these occur, offer oral calcium supplementation or administer intravenous calcium gluconate (0.5ml/kg 10% calcium gluconate)

There may be platelet loss during the procedure. A post procedure FBC and HbS% are mandatory post procedure tests.

Specific complications

Hyperviscosity

This may result in neurological deterioration, such as seizures, and can lead to worsening of the clinical condition.

- **Always** check the post transfusion haematocrit and maintain <0.35

Metabolic disturbance

These include hyperkalaemia, hypocalcaemia (due to citrate toxicity), hypernatraemia and glycaemic disturbance.

- Be aware of these complications and check a biochemical profile after the procedure and correct as necessary.

Delayed haemolytic transfusion reaction (DHTR)

Sickle cell patients are at higher risk of DHTR due to an increased rate of alloimmunisation.

In order to mitigate this risk, the following should occur:

- A transfusion history should be documented for all patients and blood bank informed if there are any issues. A baseline group and screen should be performed on all new patients.
- Blood bank will check SPICE records for all patients with sickle cell diease requiring a transfusion who have not previously been transfused in this trust.
- Any patient presenting within 7-14 days after a transfusion with signs of a crisis should be investigated for evidence of DHTR
- Any patient with a newly identified allo-antibody associated with a DHTR should be given an antibody card and the event reported to SHOT.

Hyperhaemolysis

This is a well-recognised but rare complication of blood transfusion in patients with sickle cell disease.

It is characterised by rapid haemolysis following a transfusion, leading to the destruction of transfused and autologous blood. It may be associated with a DHTR but may occur with no evidence of new red-cell antibody formation.

Clinical features and diagnosis:

- **FBC**: Hb often falls to below pre-transfusion levels
- **Reticulocyte count**: May be raised (active haemolysis) or falls due to suppression of red cell production
- **HPLC**: HbA% falls and often becomes absent (leading to rise in HbS%)
- **DAT**: To assess for new alloantibody formation.
- **G&S**: To assess for new alloantibody formation. Consider requesting eluate studies.

Treatment:

Management depends on the severity of anaemia and speed of haemolysis. Further transfusions should be avoided, but may be required if profound anaemia exists.

In severe cases, early administration of intravenous immunoglobulin and methylprednisolone is recommended (Immunoglobulins should be requested in line with UHL policy). Supportive care involves the following:

- Recombinant erythropoietin to avoid the need for further transfusion (options include NeoRecormon 300units/kg SC daily for 5 days).
- IV iron (review with appropriate results)
- B12/Folate supplementation

Eculizimab® is commissioned for use in hyperhaemolysis where the clinical criteria as laid out in the commissioning document are met. This information is available here: https://www.england.nhs.uk/wp-content/uploads/2020/09/1821_Rituximab_Eculizumab_Clinical_Commissioning_Policy.pdf

The decision to give eculizumab +/- further transfusion should be taken by a consultant Haematologist, with expertise in Haemoglobinopathy where possible. In line with the commissioning document, all cases must be discussed at the National Haemoglobinopathy Panel for retrospective approval. This will be facilitated by the UHL specialist haemoglobinopathy team.

Recurrence of hyperhaemolysis is unpredictable but can occur, even after several years. Decisions regarding future transfusions should be made by the haemoglobinopathy team.

Appendix 1: BSH indications for transfusion

Table I. Indications for blood transfusion in sickle cell disease.

Indications where primary goal of transfusion is to correct acute anaemia	GRADE evaluation	Type of transfusion*
Aplastic crisis	1B	Simple (top up)
Acute splenic sequestration	1B	Simple
Acute hepatic sequestration	1B	Simple
Delayed haemolytic transfusion reaction (transfusion should be avoided unless the anaemia is severe or life-threatening)	1C	Simple
Indications where primary goal of transfusion is to reduce HbS concentration in relation to HbA	**GRADE evaluation**	**Type of transfusion***
ACS	1B	Simple or exchange†
Acute stroke or other neurological deficit (e.g. TIA)	1B	Exchange
Acute multi-organ failure	1C	Exchange
Mesenteric/girdle syndrome	1C	Exchange
Severe sepsis	2C	Exchange
Acute intrahepatic cholestasis	1C	Exchange
Primary stroke prevention	1A	Simple or exchange
Prevention of silent cerebral infarct recurrence	1A	Simple or exchange
Secondary stroke prevention	1B	Simple or exchange
Surgery		
• SS patients – elective low or medium risk surgery	1A	Simple or exchange
• SC patients – elective low or medium risk surgery	1C	Exchange
• All sickle genotypes – elective high risk surgery	1C	Exchange
• Emergency surgery	1D	Individual considerations‡
Pregnancy		
• Sickle complications (e.g. painful crises, ACS, stroke)	1B	Simple or exchange
• Severe anaemia	1C	Simple
• High obstetric, medical or fetal risk	1C	Simple or exchange
Recurrent ACS§	2C	Simple or exchange
Recurrent painful crises§	2C	Simple or exchange

Appendix 2: Process for manual exchange (adapted from STSTN guideline)

Equipment:

High flow venous access – either via standard femoral line or vascath (apheresis line), or large vein cannula if patient has two large bore veins accessible. (Minimum grey or orange venflon)
Sterile pack, gloves etc
20-60ml syringes
3- way tap
Venesection bags
Large sharps bin

Methods:
NOTE: The blood must be checked by two trained people, and the hospital Transfusion Policy must be followed. Ensure that the details on the compatibility label (tag) on the blood bag match those on patient's wristband and prescription chart.

1. Set up a normal saline infusion 1l and run 500mls over 15 to 30 minutes to ensure pre- hydration before the procedure.

2. Ensure that the blood to be transfused is set up before venesecting the patient, to avoid hypotensive emergencies and to ensure a degree of warming of the blood prior to transfusion.

    a. The procedure should be performed more slowly than described in patients with significant renal or cardiac abnormalities, or if acutely cardiovascularly unstable.
    b. The patient should be kept in overall fluid balance throughout the procedure. This may require the infusion of additional saline if small units of blood are provided.

3. To venesect: remove 450-500ml of blood over approximately 15-30 min

    a. Blood can be aspirated from the line using 20-60ml syringes, which can either be discarded in a **fresh** sharps bin – and easily counted if necessary – or using a 3-way tap expel the contents into an attached venesection bag.

4. Calculate the amount to be exchanged, depending on starting haemoglobin, as follows:
    Hb >8.0g/dl 5-8 units
    Hb 6-7.99g/dl 4-6 units
    Hb <6 g/dl up to 4 units

5. Proceed as follows:

If Hb >8.0g/dl
Venesect 1st unit WHILST Replacing with 500 mls of normal saline stat
Venesect 2nd unit THEN Transfuse 1st unit over 30-40 minutes. *
Venesect 3rd unit THEN Transfuse 2nd unit over 1hour
Venesect 4th unit THEN Transfuse 3rd unit over 2 hours
Check FBC and Hb S
If Hb<9g/dl Transfuse 4th and consider 5th units (over 3 hours each)
If Hb>9g/dl Restart from "venesect 1st unit"

NB This method involves removing 2 units of blood before transfusing the 1st replacement unit, and results in a more efficient lowering of HbS%. However if the patient is cardiovascularly unstable, or becomes hypotensive during the venesection, the replacement transfusion should be started sooner, ie after the venesection of the 1st unit.

If Hb 6 – 7.99g/dl
Venesect 1st unit Transfuse 1st unit.
Venesect 2nd unit Transfuse 2nd, 3rd and 4th.
Further exchange may be required (see "Hb 8.0-10g/dl") if insufficient clinical improvement/impact on HbS%.

If Hb < 6
Top up transfusion to Hb 8-10g/dl (over 90 minutes to 3hours per unit depending on clinical condition).
Formal exchange may be required (see "Hb 8.0-10g/dl") if insufficient clinical improvement/impact on HbS%.

3. Education and Training

Blood transfusion training as part of mandatory training.

Mandated induction training session for newly appointed haematology ST3 trainees.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Red cell transfusions in patients with sickle cell disease	Audit	Dr Amy Webster	Annually	Audit report to CMG quality lead
ST3 induction meeting	End of induction report	Dr Amy Webster	Each induction period	Pathology quality lead

5. Supporting References (maximum of 3)

Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects Davis et al on behalf of the British Committee for standards in haematology *British Journal of Haematology* 2017;176(2):179-191

Guidelines on red cell transfusion in sickle cell disease. Part II: indications for transfusion Davis et al on behalf of the British Committee for standards in haematology British Journal of Haematology 2017;176(2):192-209

Standards for the clinical care of adults with sickle cell disease in the UK. 2nd Edition, 2018

6. Key Words

Sickle cell disease, transfusion, hyperhaemolysis

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Dr Amy Webster – Consultant Haematologist	**Executive Lead**
Details of Changes made during review: Reference to process for access to out of hours red cell exchange	