Supporting the transfusion needs of patients with inherited red cell disorders during the COVID-19 pandemic in England: A phased approach.

Haemoglobinopathy Coordinating Centres, Clinical Reference Group for Haemoglobinopathies and NHS Blood and Transplant consensus document.

6th April 2020 v1

This document has been produced to provide guidance during the COVID-19 epidemic. Many patients are "shielding" due to hyposplenism, cardiac iron, asplenia or other complications of their condition. We don't want patients to attend hospital unless they absolutely must; and ultimately, we may face shortages in blood supply. Immense thought and consideration has gone into the recommendations and they reflect a consensus of clinicians' views based on our understanding of COVID-19 at the time of publication. In light of the accruing dataset in these patients, we intend to review and amend these recommendations as we learn more about the effects of COVID-19 on our patient cohort .Patients with inherited haemoglobin disorders will be prioritised for blood during a shortage as outlined in the National Blood Transfusion Committee Red Cell Shortage Plan https://www.transfusionguidelines.org/uk-transfusion-committees/national-blood-transfusion-committee/responses-and-recommendations. This document provides guidance on how blood use could be reduced in this patient group to help ensure there is sufficient supply for all patients that need it.

Clinicians should review the notes, regimens and transfusion parameters of all patients on long term transfusion therapy to consider where they can reduce blood usage and hospital attendances. Ideally these decisions should be explained to patients wherever possible. A proforma to document these discussions are noted in Appendix 1. All amendments to current laboratory practice will need to be coordinated with the lead consultant for transfusion and the Chief Biomedical Scientist in the hospital transfusion laboratory.

Definitions:

Haemoglobinopathies: Sickle cell disease (homozygous and compound heterozygous NOT carriers NOT trait). Thalassaemia (transfusion dependent and independent, NOT carriers NOT trait).

Transfusion dependent anaemias: Diamond Blackfan Anaemia, Congenital dyserythropoeitic anaemia, congenital sideroblastic anaemia, other red cell disorders e.g. pyruvate kinase deficiency ONLY if transfusion dependent.

PHASE 1: Red cell stocks are reduced but adequate for most scenarios

All the following points should be considered or acted upon as of the date of issue of this document.

	Discussion Point	Discussion	Recommendations
1	Age of blood requirements for patients with haemoglobinopathies	Rationale for their existence is that it will increase the longevity of the donor blood in the circulation. Rationale for their (temporary) removal: the age of blood especially for sickle is very constraining and may lead to blood not being available. The impact of delayed transfusion outweighs the risk of an older unit of blood. There is some concern that as older blood has higher supernatant potassium this might be problematic in large volumes. However, large volumes are only given rapidly in automated exchange transfusion where the process results in a temporary depletion in electrolytes. Older	Stop mandatory age of blood requirement for patients with haemoglobinopathies and transfusion dependent anaemias if fresher red cells are not available.

		blood is occasionally used in emergencies in automated exchange transfusion and in those who have difficult to match blood and no such cases of symptomatic hyperkalaemia have been reported to Serious Hazards of Transfusion (SHOT) haemovigilance scheme in this setting.	
2	Group and Save (G+S) to transfusion time interval for patients with thalassaemia	Published data has demonstrated that 1 week is safe in transfusion dependent thalassaemia, this is published and is in standard practice at the two largest thalassaemia units in the UK. The data on patients with non-transfusion dependent thalassaemia suggests a higher risk of alloimmunisation, but this patient group are not regularly transfused so the interval issue is not problematic in this setting. The data for other transfusion dependent anaemias is not there, but in those without alloantibodies a 1week group and save to transfusion time interval seems reasonable in this setting.	Make as standard 7 days G+S to transfusion time in transfusion dependent thalassaemia in your hospital. Make as standard 7 days G+S to transfusion time in transfusion dependent anaemias if they do not have antibodies in your hospital.
3a	Group and Save to transfusion time interval for patients with sickle cell disease – extending the interval	Concern is that an antibody may develop in the gap between the sample and the transfusion. There is evidence for the following:	Consider extending the G+S sample to transfusion time to 96 hours or a week in patients with sickle cell disease who have no alloimmunisation and have had 100 units of blood. This will allow Friday pm samples to be

		a. A responder phenotype in SCD whereby some patients seem to be prone to making antibodies and others do not. b. That alloimmunisation risk is greater if you have episodic rather than regular transfusions c. That those who are not alloimmunised after repeated transfusions are very unlikely to become so. d. The rate of new alloimmunisation in those on regular exchange transfusions is low Other points: Canada has a 96-hour G+S policy A 72-hour policy has resulted in most transfusions for sickle cell patients occurring Wednesday – Friday in England (NHSBT data) as samples are not taken on the weekend. This puts significant pressure on ABO, Rh c, C, D, e, E and K matched HbS negative blood on those days as well as an increased chance of having an Ro substitution. BSH compatibility guidelines state: A formal deviation from the 3-day rule may be considered for **chronically transfused patients with no alloantibodies**, following multiple repeated transfusion episodes, allowing samples to remain acceptable for up to 7 days. However, alloimmune response to red cells is unpredictable	used for transfusions on Monday and Tuesday.

		and may be first detected after many transfusions……Great care should therefore be taken, and there should be a formal assessment of risk and benefit for each patient undertaken by a haematologist as part of their management plan, and this should be recorded on the LIMS and documented in the patient's record. Each individual assessment should be reviewed on an annual basis, or immediately in the event of a change in serological status. An automated exchange in an adult uses 10 units on average every 6 weeks so by a year they should have had 100 units.	
3b	Group and Save to transfusion time interval for patients with sickle cell disease – same day crossmatch	It may be feasible to crossmatch on the same day as a transfusion episode This is more likely where the patient does not require an IAT crossmatch; where the transfusion episode is in the afternoon; where the laboratory is on-site. By only coming in for once (rather than twice for a separate day G+S and transfusion) then you decrease the amount of time people are on transport, however, you increase the time spent in hospital whilst waiting.	Offer patients the opportunity to attend for a G+S sample on the same day as their transfusion if the risk to infection to the patient is deemed less due to a reduction in transport time vs. time spent in hospital waiting for sample processing and units to be released. As with all planned transfusions suitable blood should be pre-ordered for these patients.
4	Keeping of appointments and reminders	Patients with SCD are mostly transfused as primary or secondary stroke prevention. This is	Use electronic reminders and/or phone calls for patients to alert them

		often associated with poor executive function. Non-attendance for blood tests or transfusion can be common and result in blood wastage.	to their appointments. Have a mechanism of letting the Transfusion Laboratory know if the transfusion is being deferred due to non-attendance so that the blood can be reallocated.
5.	Use of depletion exchange	This is a procedure by which red cells are removed from the patient and saline infused during the initial phase of the exchange on the Optia. There are two modes on the Optia – depletion exchange and exchange. The depletion exchange mode can be set to 3% or 6% depletion. It will result in a temporary reduction in haemoglobin levels; however, the machine will still achieve the results that you ask it to. This is similar to how you conduct a manual exchange i.e. at the start of the exchange, saline flows into the patient and blood out. If you do not think the patient will tolerate a 3% or 6% depletion as cannot tolerate a lower haemoglobin, depletion exchange is not suitable. If you are incrementing the final haemoglobin as part of the exchange procedure often depletion exchange mode often does not result in less blood being used.	In those patients you think may tolerate a temporary reduction in haemoglobin due to a 3% or 6% depletion then input their data into the Optia machine and select depletion and then exchange. Then repeat the process and just select depletion. Check to see which one uses less units of blood. Staff should be reassured that this is a non-aerosol generating procedure. Those who are unfamiliar with depletion exchange can get support from the machine manufacturer Terumo, and from centres who have been using this procedure for some time.
6.	Law of diminishing returns	Reducing the sickle cell percentage to very low levels (<15%) in automated red cell exchange starts using very significantly more units of bloods to achieve a further smaller decrease in HbS%.	For a standard red cell exchange in an emergency a target HbS% of 20 should be satisfactory.

		This is because you are "wasting" much of the blood (HbA) you transfused, as the machine works on the fraction of cells remaining and cannot differentiate between HbA and HbS.	For those on long term programmes who are failing to keep their peak HbS% low enough, on a case by case basis, consider the following: - Increase the Hb at the end of the exchange – this can be done by a post exchange top up. - A reduction beyond a target HbS% of 15 – consider a post exchange top up. Note that the Hb at the end of the top up should be within limits of safety for that patient (usually not >110g/l and not an increment of haemoglobin >40g/l in a day)
7	Use of top up transfusion in sickle cell disease	Top up transfusion in those whose haemoglobin is sufficiently low may mitigate the need for an exchange transfusion in those with incipient chest crisis or those who are on regular exchanges, although if used in the long term will result in iron loading.	Consider top up transfusion in those who may well manage without an exchange for example if Hb <90g/l as a blood saving mechanism
8	Use of hydroxycarbamide in sickle cell disease	Hydroxycarbamide has been shown to decrease the severity and frequency of crises in SCD, and to reduce the need for blood transfusion (in the original MSH study). Crises in SCD can lead to a need for a blood transfusion.	Consider starting patients with SCD on hydroxycarbamide who have significant disease phenotypes where you think the frequency of blood test monitoring may be less than that of acute admissions due to complications of their disease.

		Patients with SCD who are on hydroxycarbamide who become unwell are less likely to need a transfusion during that episode than those not on hydroxycarbamide. For those who have had an abnormal TCD, have been maintained on transfusions for >18/12 and have a normal MRI/A there is no advantage of transfusion over hydroxycarbamide. Starting hydroxycarbamide requires blood tests and monitoring, however, those with higher resting platelets and neutrophils are unlikely to become thrombocytopenic or neutropenic on lowish doses. It takes a while for hydroxycarbamide to exert its full beneficial effect (weeks/months). Sperm saving and analysis is often recommended for men starting hydroxycarbamide.	Optimise dosing for those on hydroxycarbamide and ensure adequate supplies. Consider extending blood testing to 4-monthly to perhaps even 6-monthly (from BSH guidance of 3 months) in those who are on a stable dose of hydroxycarbamide and are compliant. A risk benefit analysis should be performed balancing the risk of attending for a blood test vs. the likelihood of concerning blood results. Ask hospital pharmacies if they can send out the hydroxycarbamide to patients. Although sperm saving and analysis is often recommended for men starting hydroxycarbamide this may not be available during the COVID-19 epidemic. This should be discussed with patients.
9	Further considerations of the use of automated exchange in a patient who may have COVID-19 and are undergoing aerosol generating procedures	An automated exchange lasts 2-3 hours of close contact with the apheresis nurse to the patient.	Consider top up transfusion if it may achieve the same outcome as an exchange in a patient who has COVID-19 particularly if they are

		Femoral access allows the machine and thus the nurse to be placed at the end of the bed >2m away from the head during the procedure. NIV, suction and several other procedures in ITU settings are aerosol generating increasing the risk of infection to staff.	undergoing aerosol generating procedures In those who need automated exchange whilst undergoing aerosol generating procedures, femoral access is optimal.

PHASE 2: Prioritisation Model of those on regular transfusion in the event of a red cell shortage and to mitigate risks of attending hospital in a population who are 'shielding'.

Note at the time of writing a. there are good national blood stocks and b. The National Blood Transfusion Committee Red Cell Shortage Plan file:///C https://www.transfusionguidelines.org/uk-transfusion-committees/national-blood-transfusion-committee/responses-and-recommendations has indicated that patients with SCD, thalassaemia and other inherited transfusion dependent anaemias would be prioritised in a blood shortage.

The priority setting below has been drafted because at the time of writing, very few of the authors are deployed to continual front-line work and are supported by junior doctors. With the evolving COVID-19 situation this is likely to change.

Clinical teams should consider from the date of publication of this document, which of their patients fall into which category, so should a severe red cell shortage occur, and NHS Blood and Transplant, despite prioritising this cohort cannot supply blood in the volumes that we need for our patients, this policy can be enacted swiftly. There is an immense amount of work being undertaken to ensure sufficiency of supply in this scenario, so this is a precautionary prioritisation model that we hope not to enact.

Priority Level	Patient cohort	Discussion	Recommendations
1	Those who are at high risk of significant harm if blood transfusion not administered within the same week	Sickle with significant cerebral vasculopathy, recent stroke with HbS% target <30%. Sickle with very severe disease/co-morbidities (e.g. renal failure, severe respiratory disease). Transfusion dependent thalassaemia with significant pulmonary hypertension or other cardiopulmonary disease	These sickle patients probably need to continue with current practice (whilst incorporating where relevant the measures in Phase 1) Prioritise blood provision (could delay by a few days if blood shortage) Prioritise day unit attendance/admit for transfusion if day unit shut. Link closely with your Transfusion Laboratory regarding your requirements and ask that they

			discuss with NHSBT as early as possible to give the best chance of meeting transfusion requirements
2	Those at risk of harm if transfusion significantly delayed but may tolerate less blood or an extended interval e.g. by a week or in rare cases two.	Transfusion dependent thalassaemia and other transfusion dependent rare anaemias e.g. PK, DBA. SCD transfused due to recurrent pain/ACS, frequent attenders, other co-morbidities. These patients are likely to be admitted with crisis if we delay. They are at higher risk of chest complications with infection Secondary stroke prevention – target HbS% <50% There is a risk of re-stroke if we delay – but risk less than for priority 1 patients	Consider extending interval Transfuse if possible – could delay for 1-2 weeks if blood shortage If need to cancel, rebook within 1-2 weeks. If there is blood shortage, in DBA patients delay transfusion by one to two weeks and allow Hb to drop to 80 g/L
3	Those who are on regular transfusion but may well tolerate other treatments or may manage without and are shielding	Those on regular transfusion for frequent VOC but no severe comorbidities and not a frequent attender.	Consider starting hydroxycarbamide or substituting top up transfusion. Postpone if blood shortages Rebook once situation resolves or stabilises

Appendix 1: Example documentation of Patient Discussion Regarding Transfusion during COVID-19 Outbreak

XX was reviewed on the haematology day unit/over the phone to discuss their transfusion plan during the Covid-19 outbreak.

We discussed the current situation with Covid-19 and the situation with shielding

We explained that the latest government guidance strongly advises people with serious underlying health conditions to rigorously follow shielding measures and this includes people with sickle cell disease https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19

There is additional advice on the Sickle Cell Society website: https://www.sicklecellsociety.org/coronavirus-and-scd/ and on the Trust website.

The balance of risks and benefits of continuing their transfusions has been discussed with them. Also discussed were some of the measures we are taking to use blood more effectively and minimise hospital attendances. The risks of visiting hospital during this time have been balanced against the benefit they will obtain from transfusion. We have also discussed that we may need to delay their transfusion, or deliver using an alternative modality, or change their transfusion targets/timings due to lack of staff or shortages in the blood supply chain.

Issues discussed:

Current transfusion regime

Indication (and priority)

Frequency

Pre-transfusion and HbS%

Venous access

Options considered

Stop transfusion

Decrease frequency /delay transfusion

Change to hydroxycarbamide

Top up instead of exchange

Plan for next 12 weeks.

Plan if lack of staff/blood supply

Also discuss

Medication provision

Travel to hospital

Same day bloods /phlebotomy provision

Support at home

Reschedule any outpatients

What to do if they have symptoms

Any other health issues

Outstanding issues (post COVID-19)