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How I manage red cell transfusions in patients with sickle cell disease

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Summary

Sickle cell disease is one of the commonest serious inherited diseases in the world, and red cell transfusion is still one of the few effective treatments for acute and chronic complications. Transfusion corrects anaemia and dilutes out the number of red cells able to cause vaso-occlusion and vascular damage. Urgent red cell transfusions are used to correct acute anaemia, treat acute chest syndrome and patients with acute neurological symptoms. We use elective transfusions preoperatively for moderate risk surgery, and in some pregnant women. There is good evidence for the use of long-term regular transfusions in primary stroke prevention, with the aim of keeping the percentage of sickle haemoglobin below 30%. Long-term transfusions are also used in secondary stroke prevention, and the management of progressive organ damage, including renal impairment and pulmonary hypertension. Blood needs to be matched for ABO, RH and Kell, although alloantibodies may still develop and require more careful, extended cross-matching. Delayed haemolytic transfusion reactions are relatively common, difficult to diagnose and manage, and potentially fatal.

Keywords: sickle cell disease, transfusion, haemolytic transfusion reaction.

Sickle cell disease (SCD) is one of the commonest severe inherited disorders in the world, with about 300 000 affected babies born annually. Each year, approximately 90 000 are born in Nigeria, 44 000 in India, 40 000 in Democratic Republic of Congo, 12 000 in USA, 2000 in Europe and 300 in the United Kingdom (Piel *et al*, 2013). Although UK numbers are dwarfed by those in Africa, more than 10 000 affected individuals live in the UK, making it much more common than cystic fibrosis or haemophilia A (Brousse *et al*, 2014a). Just as prevalence varies widely with location, so does clinical severity. Median life expectancy with SCD in the UK is thought to be greater than 60 years now (Gardner *et al*, 2010), whilst 80% die in childhood in much of Africa (Rees, 2014). Treatment options are limited, particularly in low-income settings.

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Pathophysiology of SCD and it relevance to blood transfusions

There are approximately 15 different types of SCD, and all of them include at least one copy of the sickle mutation (β^s) in the β globin gene (*HBB*; c.20A>T, p.Glu7Val). The most common and severe form of SCD is caused by homozygosity for the β^s mutation, usually referred to as sickle cell anaemia (SCA). The other important types of SCD occur when β^s is co-inherited with either a β-thalassaemia mutation (HbS/β thalassaemia) or the haemoglobin (Hb) C mutation (*HBB*; c.19G>A, p.Glu7Lys; HbSC disease). In all types of SCD, the fundamental pathophysiological process is the polymerization of the deoxygenated Hb molecule. These polymers can form very rapidly, damaging the red cell membrane, causing cellular dehydration and rigidity These damaged red cells cause vaso-occlusion and many secondary pathological processes, including inflammation (Zhang *et al*, 2016), haemolysis (Hebbel, 2011), anaemia, vasculopathy and oxidative stress; (Brousse *et al*, 2014a).

SCD is characterized by intermittent, acute and largely unpredictable episodes of acute illness, mostly related to acute vaso-occlusion causing ischaemic pain and organ dysfunction, such as acute chest syndrome (ACS); the Hb level may fall during these acute episodes. These acute problems occur on a background of chronic, progressive vasculopathy and organ damage which starts in early infancy with hyposplenism (Brousse *et al*, 2014b), and continue throughout life causing renal impairment, pulmonary damage, bone disease, cerebrovascular disease and premature death (Brousse *et al*, 2014a; Elmariah *et al*, 2014).

Of relevance to blood transfusion, SCD usually causes some degree of anaemia, which can be very mild in HbSC disease (Rees *et al*, 2015) or relatively severe in SCA, with a mean steady-state Hb of 70–80 g/l, and a range of 50–100 g/l. Typically, patients adapt well to this steady-state anaemia, and blood transfusion is rarely used to correct chronic anaemia *per*

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se, although there is increasing evidence that chronic anaemia may contribute to some complications, including cerebrovascular disease and pulmonary hypertension. The origin of the anaemia is multifactorial, but predominantly caused by haemolysis, as intrinsic erythrocyte damage and vaso-occlusion lead to reduced red cell survival; other contributory factors include ineffective erythropoiesis, impaired iron utilization, an impaired erythropoietin response and low oxygen affinity of the HbS molecule (Sherwood *et al*, 1986). Overall the causes and mechanisms of anaemia in SCD are poorly understood and not the subject of that much research.

Blood transfusion has two direct potentially beneficial effects in SCD: the correction of anaemia and the dilution of red cells containing HbS. The correction of anaemia is straightforward and predictable, and improves oxygen carrying capacity, which, depending on the changes in blood viscosity, may improve (or impair) oxygen delivery to tissues. The dilution of HbS-containing erythrocytes is likely to reduce the tendency to vaso-occlusion, although the exact benefits will vary depending on (poorly understood) rheological factors, including the size of the blood vessel and tissue oxygenation. The benefits of transfusion are countered by the increase in haematocrit and whole blood viscosity, which occur with increasing Hb (Rackoff *et al*, 1992). Based on fairly crude experiments, oxygen delivery is thought to fall once the haematocrit gets above about 0·35 in SCA blood (Fig 1), although this will vary depending on blood velocity, oxygenation and vessel size (Jan *et al*, 1982). There is little experimental evidence to support current clinical practice, and it is certainly possible that blood transfusion to a certain level might improve oxygen delivery in the brain whilst impairing pulmonary oxygenation, for example. Given the lack of evidence, transfusion practice in SCD is largely based on empiricism and physiological principles.

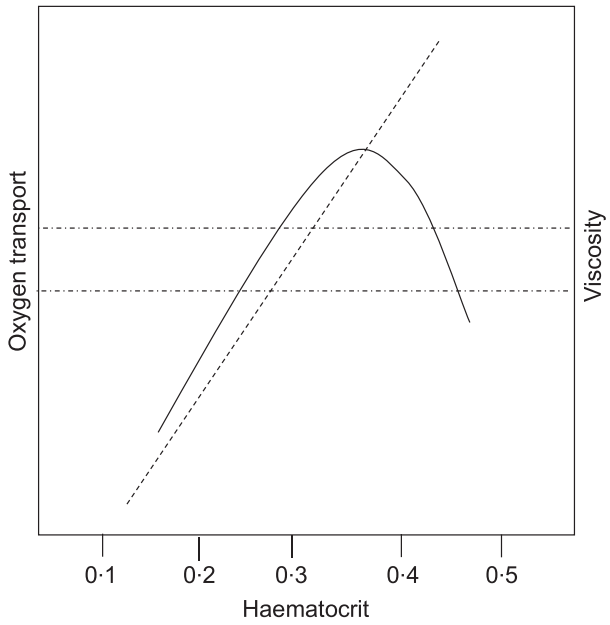

Fig 1. Diagrammatic representation of the relationship between haematocrit, whole blood viscosity (dotted line), and oxygen transport (solid line) in whole blood in HbSS at venous oxygen tension. The horizontal dotted lines define the normal range of blood viscosity. Based on coaxial measurements of whole blood viscosity taken from patients before and after blood transfusion. The figure shows that with increasing haematocrit, oxygen transport increases up to a point, after which it falls due to increased blood viscosity (adapted from Jan *et al*, 1982).

Blood transfusions in the management of acute complications

We note that, apart from the role of transfusion for the prevention of neurological complications of SCA, there is little randomized controlled evidence to guide clinicians on when to offer transfusion. We also note a general lack of disease modifying treatments for patients with SCD, with hydroxycarbamide (also termed hydroxyurea) as the only licensed treatment in the UK for the long-term prevention of disease complications. The indications for transfusions in SCD have recently been reviewed by Davis *et al* (2017) and further discussion can be found there.

Acute anaemia

We offer simple transfusion, aiming for a post-transfusion Hb to baseline levels, for patients with symptomatic acute anaemia, irrespective of aetiology (e.g. transient erythroblastopenia due to human erythrovirus B19, splenic or hepatic sequestration (Brousse *et al*, 2014b), rapid haemolysis, severe vaso-occlusion, malaria, influenza and other infections), when the Hb level has fallen significantly (>20 g/l) below their baseline. Symptoms and signs suggesting the need for transfusion include faintness, breathlessness, increasing tachycardia and increasing dyspnoea.

Acute pain

In acute pain, pilot randomized trial data showed no benefit of transfusion on the length of hospital stay, total opiate use or daily pain score (Kelly *et al*, 2015); although this was a small study which stopped before recruitment was complete. Interestingly, an observational study of adult SCD patients admitted to hospital with acute pain showed that blood transfusion was associated with a reduced odds ratio of inpatient mortality and 30-day re-admission rate, although these data can be interpreted in many different ways (Nouraie & Gordeuk, 2015). We do not routinely offer transfusion to patients with acute pain, although we may consider it where there is a marked decrease in Hb or where pain is intractable.

Acute neurological events

Exchange transfusion is the treatment of choice for patients presenting with acute ischaemic stroke, with a small

retrospective study suggesting that it may be associated with a lower risk of recurrence than simple transfusion (Hulbert *et al*, 2006). We may consider an initial simple transfusion if the patient presents with an ischaemic stroke and marked anaemia (Hb < 60 g/l), and this would be followed by an exchange transfusion. An urgent top-up transfusion may also be helpful to correct anaemia rapidly if there is going to be a significant delay (>6 h), before the exchange can start. The role of thrombolysis and aspirin is unknown in both adults and children. It may be appropriate to gain venous access, then give thrombolysis, then perform exchange transfusion, but this needs to be studied.

There is little evidence on how to manage acute haemorrhagic stroke in SCD, although again, exchange transfusion, with target of reducing the HbS levels below 30% (or HbS+Hb C < 30% in HbSC disease), is usually performed early in the course of management, with a view to protecting the brain against ischaemic damage and reducing the risks of any operations or investigations. Urgent neurosurgical management takes priority over blood transfusion, although blood loss perioperatively may effectively mean that exchange takes place during surgery.

In general, any patient presenting with new, unexplained focal neurological signs should be considered for urgent transfusion, potentially with a target HbS of less than 30%.

Acute chest syndrome (ACS)

The role of transfusion in ACS (Vichinsky *et al*, 1997) is outlined in a recent guideline (Howard *et al*, 2015) and whilst both simple and exchange transfusions seem to be associated with improved outcomes, not all patients with ACS will require transfusion. Less severe cases, particularly children with predominantly infective aetiology, are very likely to recover with supportive care, including antibiotics and incentive spirometry. There are no randomized trials comparing simple, exchange or no transfusion and it is unclear if there is benefit of exchange over simple transfusion. We support the pragmatic approach suggested by the British Society for Haematology guidelines, which is to consider simple transfusion for patients who have worsening anaemia (Hb level 10 g/l or more below their baseline), or oxygen saturations (below 93% on room air) or increasing oxygen requirements. Exchange transfusion should be considered if patients deteriorate despite initial simple transfusion, if they have features of severe disease (worsening hypoxia, increasing respiratory rate, decreasing platelet or Hb level, multilobar involvement on chest X-ray and neurological complications) or require mechanical ventilation.

Other indications for acute transfusion

Transfusion probably has a limited role in the treatment of acute priapism, with observational studies showing variable response to transfusion (McCarthy *et al*, 2000; Ballas & Lyon, 2016). Anecdotal reports have also suggested an increased risk of neurological events associated with exchange transfusion for priapism, including headaches, seizures and reduced levels of consciousness (Siegel *et al*, 1993). We limit the use of transfusion to those cases which have not responded to initial treatment with pain relief, alpha-adrenergic medication, aspiration and irrigation and require definitive shunt surgery.

There are case reports and small series suggesting the efficacy of exchange transfusion in patients who are acutely unwell with life- or organ-threatening complications, either primarily related to SCD (acute sickle hepatopathy) (Sheehy *et al*, 1980; Marti-Carvajal & Marti-Amarista, 2017) or unrelated (severe sepsis, multi-organ failure) (Cottin *et al*, 2014). These severe illnesses are associated with many factors that promote HbS polymerization, including both general and regional acidosis and hypoxia, and in these situations, we may consider transfusion after discussion with other specialists, including hepatologists and intensivists.

Indications for long-term transfusion (chronic transfusion)

Primary and secondary stroke prevention

The majority of randomized trials utilising transfusion as an intervention have looked at primary stroke prevention. Chronic transfusion certainly significantly decreases the risk of stroke in children with raised trans-cranial Doppler (TCD) velocities (Adams *et al*, 1998). The initial study suggested a 90% reduction for stroke risk in children with TCD velocities >200 cm/s if the HbS was maintained at less than 30%, and this has largely been borne out by real-world data when used as part of routine clinical practice (Fullerton *et al*, 2004; Bernaudin *et al*, 2011). It is not clear how long transfusion should be continued in these children and whilst the STOP (Optimizing Stroke Prevention in Sickle Cell Anemia) 2 trial showed that stopping after 30 months of transfusion leads to a recurrence of stroke risk (Adams & Brambilla, 2005), it is unclear if transfusions can be safely stopped beyond this and if any benefit persists into adulthood.

There are many different ways to maintain the HbS level below 30% using regular transfusions, and we vary our approach depending on the patient. In younger children weighing less than 30 kg, we typically use simple transfusions every 3–4 weeks, whereas in older children and adults exchange transfusions are used. We monitor the HbS levels, pre-transfusion Hb, iron levels and neurological status in monthly meetings and adjust the regimen to achieve targets. If the HbS% is too high we either increase the frequency of transfusion or the post-transfusion Hb target. If there is evidence of progressive cerebrovascular disease despite optimal treatment, we intensify treatment, with options including adding hydroxycarbamide (Brousse *et al*, 2013), neurosurgical revascularization or haematopoietic stem cell transplantation.

The TWiTCH (TCD With Transfusions Changing to Hydroxyurea) trial showed that hydroxycarbamide is as effective as transfusion for primary stroke prevention in children with abnormal TCDs who have received transfusions for at least 1 year and do not have severe intracranial vasculopathy, although in our experience many families choose to continue on transfusions, possibly because of familiarity and continuing concern about toxicity of hydroxycarbamide. The main advantage of switching to hydroxycarbamide is that it is less resource intense and lessens the risks of transfusional iron overload (Ware *et al*, 2016), although the children who have difficulty taking iron chelation regularly are also those at risk of not taking hydroxycarbamide. If patients choose to change to hydroxycarbamide, we establish them on a maximum tolerated dose of hydroxycarbamide, before weaning the blood transfusions. TCDs are monitored every 4–6 weeks, and transfusions restarted if abnormal velocities recur.

Long-term transfusion in children with silent cerebral infarction (SCI) also reduced the risk of further neurological events when the HbS was kept below 30% (DeBaun *et al*, 2014), and it is not known if hydroxycarbamide offers similar protection.

We offer chronic transfusion therapy to all children with abnormal TCDs, and the majority of children and families accept this. If families, for personal or religious reasons, refuse to accept regular transfusions, we persist in the offer and try to persuade them to accept this evidence-based approach. We encourage families to obtain second opinions, but if the refusal remains absolute, and there are no other concerns about safeguarding, we offer hydroxycarbamide treatment with close monitoring using TCDs and repeat brain magnetic resonance imaging (MRI)/magnetic resonance angiography. If there is any evidence of progressive cerebrovascular disease, we reassert the need for transfusion. In general we do not resort to legal action to try and enforce transfusion, because it is almost impossible to start regular transfusions against the parents' wishes without taking the child in to care, and the evidence in favour of transfusion is not so overwhelming that this action can be justified; based on the original studies of Adams, only 40% children with abnormal TCDs will have had a stroke after 10 years (Adams *et al*, 1992, 1998). We discuss conversion to hydroxycarbamide after 1 year of transfusion therapy.

The optimal management of SCI is still unclear. The Silent Cerebral Infarct Transfusion (SIT) trial suggested a modest benefit to starting transfusions in children with SCIs, with the need to treat 13 children for 3 years to prevent one recurrent infarct (DeBaun *et al*, 2014), although it is likely that all children with SCD would benefit in some way from starting regular transfusions, irrespective of the presence of SCIs. We do not routinely screen children in our clinic for SCIs, which requires MRI, and is difficult to perform in young children before the age of 6 years. We have a low threshold for performing brain MRI after the age of about 7 years, when most children can tolerate MRI without sedation or anaesthesia, and typical indications include poor school performance, frequent headaches, atypical pain behaviour or any suggestion of cognitive impairment. If MRI shows SCI we discuss the evidence with the family, including the choice of starting long-term transfusions. In our experience, if the SCIs are an isolated finding with no other concerns, the majority of children do not start transfusions, but might go on hydroxycarbamide if not already taking it; these children will be closely monitored with regular MRI scans, and the decision revisited if further SCIs develop. It is important to discuss that children with SCIs are at increased risk of overt stroke and help families take a fully informed decision. We recommend transfusions more strongly if there are any other factors suggestive of progressive or severe cerebrovascular disease, such as marked cognitive impairment, extracranial carotid artery disease (Deane *et al*, 2010; Bernaudin *et al*, 2015) or high conditional TCD velocities.

Although there are no formal trials demonstrating efficacy, long-term transfusion is the only established method of secondary stroke prevention (Cherry *et al*, 2012). Its better efficacy compared with hydroxycarbamide was shown in the Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial (Ware & Helms, 2012). We offer long-term transfusion to all children and adults who have experienced a sickle-related ischaemic stroke, which typically continues indefinitely, unless transfusion becomes impractical because of problems with multiple alloantibodies, relentless iron accumulation, very difficult venous access or personal choice. If venous access is a limiting factor we will offer the insertion of a semi-permanent venous access device, such as a Portacath, which are mostly well tolerated (Bartram *et al*, 2011). Alternatively, matched sibling haematopoietic transplantation may be a possibility, which allows transfusion to stop.

Other complications

Whilst there are no randomized trials using transfusion as an intervention for the prevention of recurrent pain or ACS as a primary outcome, the various trials looking at transfusion in stroke prevention used these as secondary outcomes. Patients receiving chronic transfusion as part of these trials demonstrated reduced episodes of acute pain and ACS (Miller *et al*, 2001; DeBaun *et al*, 2014). Hydroxycarbamide is also effective in reducing these complications and we offer this as initial treatment for prevention of recurrent acute pain or ACS, with chronic transfusion reserved for those cases where hydroxycarbamide is not acceptable or effective. The SIT trial also showed a reduction in the incidence of priapism in the group randomized to chronic transfusion so chronic transfusion may be of benefit in the prevention of recurrent priapism when initial treatment with alpha-adrenergic drugs has failed (DeBaun *et al*, 2014).

Regular transfusions are also sometimes started in young children as part of the management of recurrent acute

Table I. Our recommendations for indications for long-term transfusion in sickle cell disease. Exchange may be either automated or manual.

Complication	Simple or exchange transfusion	Comments
Recurrent pain	Exchange	If hydroxycarbamide ineffective or not tolerated. Review after 6 months
Recurrent acute chest syndrome	Exchange	Consider if hydroxycarbamide ineffective or not tolerated
Secondary stroke prevention	Exchange	
Primary stroke prevention	Exchange	Continue for at least 1 year before considering hydroxycarbamide
Leg ulcers	Simple or exchange	Consider trial of transfusion if other treatments ineffective
Recurrent priapism	Exchange	Consider trial of transfusion if other treatments ineffective
Pulmonary hypertension	Exchange	Consider on case by case basis
Post transplantation		

Table II. Our recommendations for preoperative blood transfusions.

Clinical situation	Pre-operative transfusion
HbSS or HbSβ0 thalassaemia having high risk surgery (cardiac or neurosurgery)	Exchange transfusion
HbSS or HbSβ0 thalassaemia having moderate or low risk surgery	Simple transfusion if Hb < 90 g/l Partial exchange if Hb > 90 g/l
HbSC and other genotypes having high risk surgery	Consider exchange transfusion
HbSC and other genotypes having moderate or low risk surgery	Consider simple transfusion if clinically severe and Hb < 90 g/l Consider exchange transfusion if clinically severe and Hb > 90 g/l

splenic sequestration. Practice varies, but typically, the risk of recurrence is high and preventive measures are indicated after two episodes of acute splenic sequestration requiring transfusion. The two main options are an early splenectomy, or regular, monthly transfusions until a splenectomy can be safely performed, or the tendency to sequestration has decreased. The aim of transfusion is to keep the child well without the need for emergency transfusion and we do not usually specify a particular HbS target level (Brousse *et al*, 2014b).

There are small case series showing efficacy of chronic transfusion in other indications, including heart failure, renal failure, leg ulcers (Minniti & Kato, 2016) and pulmonary hypertension (Gladwin, 2016), but in the absence of robust data, we only offer chronic transfusion for these complications on an individual patient basis and after full discussion of the benefits and risks of transfusion. Possible indications for long-term transfusion are listed in Table I.

Perioperative management

Surgery in SCD is associated with increased complications, particularly an increased risk of acute pain or ACS. A randomized trial of pre-operative transfusion *versus* no pre-operative transfusion showed a small but significant decrease in serious adverse events, particularly ACS, in patients with HbSS having moderate or low risk surgery (Howard *et al*, 2013). A previous randomized trial had shown no difference in outcomes between pre-operative simple transfusion to a Hb target of 100 g/l and exchange transfusion (Vichinsky *et al*, 1995), although most of the subjects in this study were young, and its findings may not apply to older patients with multiorgan disease.

We routinely offer simple transfusions to increase the Hb to 100 g/l in patients requiring general anaesthesia for moderate or low risk surgery. We recommend full exchange transfusion, with a target HbS of less than 30%, for patients undergoing high risk surgery (major neurosurgery, cardiothoracic) and for those with a high risk of perioperative complications, such as those with severe organ damage or a history of complications (Table II). There is less evidence for patients with other genotypes or for patients undergoing emergency surgery. In emergencies, we consider simple transfusion for patients with Hb < 90 g/l. For patients with a higher Hb level where exchange transfusion would delay the surgery it may be appropriate to proceed with surgery but to plan a post-operative transfusion if needed.

Pregnancy and transfusion

Pregnancy is also associated with increased fetal and maternal mortality and morbidity in SCD. Pregnant women should receive transfusion in the acute setting as they would outside pregnancy. There is inadequate evidence at the present time to recommend prophylactic transfusion throughout pregnancy. One small randomised controlled trial showed that acute pain episodes were decreased in pregnant women receiving prophylactic transfusion, but did not show an

impact on other fetal or maternal complications (Koshy *et al*, 1988). A meta-analysis reviewing this randomised controlled trial and additional cohort studies concluded that prophylactic transfusion was associated with a reduction in maternal, perinatal and neonatal mortality, pain episodes, pulmonary complications and prematurity but gave the caveat that the studies had a moderate to high risk of bias (Malinowski *et al*, 2015). We review all pregnant women in a joint sickle-obstetric clinic at booking and discuss prophylactic transfusion with them. We continue prophylactic transfusion in those women already receiving this and consider starting prophylactic transfusion in women pregnant with twins or with previous serious medical, obstetric or fetal complications. If women experience repeated severe pain episodes or ACS during pregnancy we offer prophylactic transfusion for the rest of the pregnancy. We start transfusions at different points during the pregnancy depending on the clinical situation and, similarly, vary transfusion targets.

Particular features of transfusions in children with SCD

Most paediatric issues are covered in the sections above. The majority of acute transfusions in children are given for ACS, and the majority of chronic transfusions for primary and secondary stroke prevention. Children are more able to tolerate large increases in Hb, and there is a greater emphasis on avoiding the need for repeat transfusion.

Different types of transfusion

For patients with SCD, red cell transfusions can be administered either as a simple (or top-up) transfusion or as an exchange transfusion; exchanges can be performed as a manual procedure with isovolumetric venesection and replacement with red cell transfusion or as an automated procedure using an erythrocytapheresis machine.

In the acute situation, we advocate simple transfusion where the patient has a low Hb, usually significantly below their baseline value, with the primary aim of transfusion to improve the oxygen carrying capacity. Simple transfusion is straightforward, can be performed in the majority of inpatient settings or in the outpatient day ward and does not require additional staff training. The majority of patients will only require peripheral venous access. A single simple transfusion will only moderately reduce the percentage of sicking (sickle %, S%), and the increasing blood viscosity limits the volume that can be transfused as the Hb is increased. Certainly for treatment of acute anaemia, the target post-transfusion Hb should be around the patients baseline and in other situations should not be increased above 100–110 g/l in a patient with HbSS (Swerdlow, 2006). Simple transfusion can be used as a long-term transfusion strategy. In this situation, particularly if it follows an initial exchange transfusion, simple transfusion can effectively suppress the S%; the risk of hyperviscosity gets less as the S% decreases and post-transfusion Hb targets can be higher (110–120 g/l) (Swerdlow, 2006). The disadvantage of long-term simple transfusion is the high rate of iron loading and patients will inevitably require iron chelation therapy after around a year of transfusion therapy.

We use manual or automated exchange transfusion in the acute situation when a rapid decrease in S% is needed, for example in patients with severe ACS or acute stroke. If we are aiming for a rapid decrease in S%, but the patient has a very low Hb (<70 g/l) we perform an initial simple transfusion followed by an exchange transfusion. An automated exchange is effective and safe for the reduction of S%, but may not be available in the emergency setting/out of hours in view of the need for specifically trained staff. A manual exchange can be used as an alternative and is relatively straightforward, in effect simply involving alternating venesection and transfusion and there are several readily available protocols (Howard & Telfer, 2015). All haematology trainees and consultants should be able to perform this procedure on adults and it should be available in all haematology units caring for patients with SCD. Children who are unwell enough to need exchange transfusion should be discussed with a specialist sickle centre and will usually require transfer to a specialist centre for exchange transfusion and access to paediatric intensive care, if needed.

For patients on long term transfusion programmes, automated red cell exchange offers several advantages over simple or manual exchange: it is potentially easier to produce lower HbS levels, it is a rapid procedure taking only 90–120 min, and can be associated with reduced iron loading and iron chelation can become unnecessary (Porter & Huehns, 1987; Kuo *et al*, 2015). Venous access may be problematic as large bore access and high rates of blood flow are required and although, in expert hands and with use of ultrasound technology, the placement of peripheral cannulas may be possible, some patients will need repeated central venous access or permanent indwelling venous catheters (Putensen *et al*, 2016). This is often particularly challenging in children and although automated apheresis is possible from around 5 years of age, many paediatric centres will not offer automated apheresis until the early teenage years. The decision to switch from top-up transfusions to exchange transfusions will depend on several factors, including patient preference, adherence to iron chelation and venous access. Furthermore, the process of automated apheresis requires access to an appropriate erythrocytapheresis machine (with an associated cost) and highly trained operators. Despite the increased costs of the automated procedure a recent technology assessment by the National Institute for Health and Care Excellence (NICE) advised that automated apheresis should be the treatment of choice for long term transfusion therapy (NICE 2016). Manual exchange can be used for long-term transfusion and can be useful to limit iron loading and maintain low HbS levels, particularly in patients with high baseline Hb

levels. However, it is time-consuming and venous access may be more complicated than for simple transfusion.

Selection of blood for patients with SCD

Alloimmunisation is a particular challenge in patients on long-term transfusions, with reported historical rates of 20–50% (Rosse *et al*, 1990; Vichinsky *et al*, 2001). Alloimmunisation is exacerbated in countries where the red cell antigen profile of the recipient population is significantly different to that of the donor population, as occurs in northern Europe and the USA (Allali *et al*, 2017). A recent review outlined antigenic discrepancies at three levels of increasing complexity: the prevalence of some common but highly immunogenic antigens differ substantially, the presence of numerous RH variants found in persons of African origin and when the recipient lacks an antigen that is expressed in almost all donor red cells (high incidence antigen) (Yazdanbakhsh *et al*, 2012). Prophylactic matching for C, E and K reduces alloimmunisation from 3 to 0·5% per unit, however extended matching for RH, Kell, Duffy, Kidd and MNS is more effective (Vichinsky, 2001; Lasalle-Williams *et al*, 2011).

Extended phenotyping and genotyping

We perform an extended phenotype, including C, c, E, e, K, k, Jka, Jkb, Fya, Fyb, S and s, in all new patients and U typing is performed in patients who are S− s−. The National Blood Service in England (NHS Blood and Transplant, NHSBT) offered extended genotyping for all haemoglobinopathy patients in England between April 2015 and June 2016, with no charge to hospitals sending the samples. A total of 4225 samples were received, accounting for approximately 42% of patients with SCD and enabling identification of RH variants. In patients for whom RH variants were identified this has enabled a more informed process regarding antigen matching of red cells in prospective transfusion plans (Chou & Westhoff, 2017). To date, we continue to request genotyping from NHSBT. The results are reviewed in a multidisciplinary meeting to determine best-matched red cell units detailed in prospective transfusion plans for each patient in the laboratory information system (LIMS).

Blood component selection

Red cells must be ABO compatible, matched for D, C, c, E, e and K antigens, antigen negative for any current or historical clinically significant red cell antibodies, HbS negative, less than 10 days old for simple transfusion and, if possible, less than 7 days for exchange transfusion (Davis *et al*, 2017). All red cell units in the UK are leukodepleted by the blood service. There is increasing evidence that matching for S is also important, particularly in African countries where K is rare (Telen *et al*, 2015). The Duffy null phenotype [Fy(a−b−)] is common in patients with SCD, and anti-Fy^a is fairly commonly found in transfused patients although anti-Fy^b is much less common. The most common RH phenotype in SCD is D+C−E−c+e+ (R_0 subtype), found in less than 2% of donors in England; the availability of R_0 blood is further limited because most of these donors are of African origin, with a relatively high prevalence of sickle cell trait. As such, due to availability, many patients are substituted units of the phenotype D−C−E−c+e+ (rr subtype). Demand has doubled to 4000 units per month in the UK and the NHSBT R_0 improvement project has increased availability, from an average of 975 units to 1970 units per month, since 2014.

Shared information regarding phenotype and alloantibodies

At various times, it has been recommended that patients should be given a card which details their red cell phenotype and information as to whether they have formed antibodies (Vichinsky, 2012). However potential risks include transcription errors and validity in the event of further alloimmunisation subsequent to card issue. Shared, updated databases seem likely to offer a better solution; for example, NHSBT has implemented 'Specialist Services Electronic Reporting using the Sunquest ICE Web Browser' for Red Cell Immunohaematology (RCI), allowing ready access to serology results and sharing of information.

Patients with multiple antibodies or requiring rare blood

The main rare blood types in SCD are in the RH (absence of Hr^s, Hr^B, or RH46), Kell (absence Js^b) and MNS (absence of U) blood groups. At least 1% of patients with SCD have the U- phenotype (Yazdanbakhsh *et al*, 2012). In the UK, U negative blood donors are extremely rare. Red cells of rare phenotypes that cannot be easily provided from current stock are stored in the National Frozen Blood Bank. There is no clear evidence on how best to manage patients who are known to be U-negative who require a transfusion. Currently we do not routinely select U-negative blood unless the patient is known to have anti-U alloantibodies. It is unknown how often U negative patients make alloantibodies to U positive blood, although this seems to happen rarely, given that 1% of transfusions in SCD are to U negative patients, and anti-U antibodies are very rare. In the event of a patient known to have anti-U antibodies requiring elective or semi-elective transfusion prior to surgery or more urgent transfusion due to an acute complication, we liaise with the blood transfusion service as soon as possible. If a transfusion seems likely, red cell units may be thawed and washed and made available on site or held centrally, although the shelf life is limited to 24 h if produced in an open system and 72 h when using the automated closed system. It may sometimes be possible to call up donors and obtain wet units, dependent upon availability. In a very urgent situation, it may be necessary to use U positive blood, with

the risk of major haemolytic transfusion reactions being very small.

For patients who have multiple antibody combinations or require blood of a rare phenotype we ensure a plan is available for the clinical team, which includes best patient blood management strategies and what to transfuse in the event the urgency or required amount of red cells changes. Dependent upon the availability of antigen negative blood in certain clinical situations, it may be necessary to transfuse least incompatible units of red cells. In the event it is not possible to provide antigen negative red cells for a patient who requires blood immediately, prophylactic steroids and/or immunoglobulin may be considered although there is not much evidence to support their use in these circumstances. In patients who have one or more alloantibodies we try to match for C, E, K, Fy, Kidd and S to reduce the risk of alloimmunisation whenever possible if this does not cause delay that might adversely affect the patient. We usually start hydroxycarbamide in patients with alloantibodies that make transfusion difficult, as it has been shown to reduce the need for transfusion (Charache *et al*, 1995).

Haemolytic transfusion reactions

The frequency of haemolytic transfusion reactions can be limited by the appropriate selection of blood for transfusion, as outlined above, although even in optimal circumstances haemolytic transfusion reactions still occur (Vichinsky *et al*, 1990).

Delayed haemolytic transfusion reactions (DHTR) are probably the most frequent and troublesome reactions. Typically, haemolysis starts between 24 h and 21 days after the last transfusion. Clinical diagnosis is difficult in that the typical features overlap with those of some acute complications of SCD, and it is difficult to be certain whether falling Hb, increasing pain and increased haemolysis are features of vaso-occlusive complications or a haemolytic transfusion reaction, or both (Scheunemann & Ataga, 2010; Gardner *et al*, 2015). DHTR should be considered as a likely explanation for any increase in pain occurring shortly after a transfusion. If relevant alloantibodies are identified this makes the diagnosis clearer, although these are often either not found or of uncertain significance. Often, alloimmune haemolysis may trigger increased vaso-occlusion and non-immune red cell destruction, causing a complex and serious situation, with a mortality of up to 10% in adults (Narbey *et al*, 2017). The term hyperhaemolysis is sometimes used to describe this sort of severe clinical picture (Win *et al*, 2001), although it is not clear that this term refers to a specific pathological process or suggests a particular treatment.

As mentioned, one of the main challenges in DHTR is making the diagnosis, and this should be suspected if there is an unexplained increase in haemolysis following a transfusion, dark urine due to haemoglobinuria or new alloantibodies are identified, possibly with a positive direct and/or indirect antiglobulin test. If DHTR is suspected, further transfusions should be avoided if possible, and serological investigations should try to identify any alloantibodies. Analgesia, antibiotics and fluids should be given as appropriate. If the Hb is falling and the patient becomes symptomatic, further transfusion is likely to be necessary, and the most compatible blood should be selected based on the patient's known blood groups and any alloantibodies identified. In some circumstances, particularly if there is known to be some degree of incompatibility of the chosen blood or a history of unexplained DHTR, we may pre-medicate the transfusion with either corticosteroids (such as methylprednisolone 10–30 mg/kg up to 1 g), intravenous immunoglobulin (1 g/kg) or both. If the haemolysis is ongoing and transfusion causes little increment in the Hb, starting rituximab may reduce haemolysis in the longer term (Gardner *et al*, 2015), although there is little or no evidence on how to best use these various options. As a general approach, the sicker the patient the more treatments they are likely to get. Severe DHTR merges into autoimmune haemolysis, which is more common in SCD and usually requires treatment with long-term immunosuppression of some sort (Aygun *et al*, 2002).

Starting and monitoring patients on regular transfusions

The target HbS percentage and pre-transfusion Hb should be established and clearly documented for all patients. Typically, the aim will be to keep the pre-transfusion HbS below either 30 or 50%, and maintain the pre-transfusion Hb above 90 or 95 g/l, although this may vary depending on the patient and indication for transfusion. Blood transfusions ideally start with an exchange transfusion to establish the HbS at or below the target level, although it is possible to achieve the HbS target with a series of two weekly transfusions, with an increasing target Hb; this latter approach is particularly useful in younger children in whom venous access for exchange transfusion is difficult. Typically, top-up transfusions are given every 3–4 weeks, and exchanges every 4–6 weeks, although again this may vary. Some children and adults will require insertion of a semi-permanent venous access device and, in general, these seem to be well tolerated with few complications (Bartram *et al*, 2011). Transfusional iron overload should be monitored, ideally using regular MRI to quantitate hepatic and cardiac iron accumulation; iron chelation should be started and monitored according to established guidelines (Porter & Garbowski, 2013).

We discuss all patients on regular transfusions at monthly multidisciplinary meetings. We review the pre-transfusion HbS percentage against the target, and modify the transfusion regime if the targets are not being achieved; typically this may involve increasing the frequency or volume of transfusions. In our experience, increasing the frequency of transfusions is the most effective way of reducing the HbS percentage. It is also important to monitor the effectiveness of the transfusions in controlling the particular indication for

transfusions, such as changes in brain MRI appearance or frequency of pain. We perform routine brain MRI every 1–2 years depending on the clinical situation. Iron accumulation is also monitored in these meetings, and uncontrolled haemosiderosis may be a reason for changing to exchange transfusions, stopping transfusions or psychological intervention (Porter & Garbowski, 2013).

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