Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects

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Blood transfusion in the management of sickle cell disease (SCD) can be lifesaving and reduces disability. However, it may cause morbidity, including alloimmunisation and iron overload (Rosse *et al*, 1990; Vichinsky *et al*, 1990; Ballas, 2001; Darbari *et al*, 2006), and mortality (Royal & Seeler, 1978; Serjeant, 2003).

A paucity of randomised controlled clinical trials has resulted in wide variations in clinical practice. However, recent randomised studies have addressed some of the outstanding issues around indications to prevent some chronic complications (DeBaun *et al*, 2014) and to prevent perioperative acute complications, such as acute chest syndrome (Howard *et al*, 2013). We have reviewed the evidence and developed two linked guidelines on transfusion in SCD; Part I relates to general principles and laboratory aspects, whereas Part II addresses indications for transfusion in SCD. Here the term SCD refers to all genotypes of the disease and sickle cell anaemia to the homozygous state (SS).

Methods

The writing group was selected by the British Committee for Standards in Haematology (BCSH) General Haematology and Transfusion Task Forces with input from other experts in haemoglobinopathy. PubMed, MEDLINE and Embase were searched systematically for publications on red cell transfusion in SCD from 1960 to May 2016 using a combination of search terms related to: (i) sickle cell (including sickle, sickle cell, SCD, sickle cell anaemia, haemoglobin SC disease, sickle cell crisis), (ii) transfusion (including transfusion, blood transfusion, red cell transfusion), (iii) transfusion indications [including aplastic crisis, parvovirus, sequestration (splenic, liver, hepatic), acute chest syndrome, stroke, silent cerebral infarcts, multi-organ failure, girdle syndrome, intrahepatic cholestasis, surgery, pregnancy] and (iv) transfusion complications (including alloimmunisation, haemolytic transfusion reactions, iron overload, viral infections). Opinions were also sought from experienced haematologists with a special interest in the care of SCD patients. The guideline was reviewed by the members of the General Haematology Task Force of the BCSH prior to being sent to a sounding board of approximately 50 UK haematologists, the BCSH and the British Society for Haematology (BSH) Committee. Comments were incorporated where appropriate. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified in the BCSH guidance pack http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html and the GRADE working group website http://www.gradeworkinggroup.org.

Summary of key recommendations

The decision to top up or exchange transfuse an adult or paediatric patient with sickle cell disease (SCD) needs the input of a clinician with appropriate experience. Specialist advice should be obtained for the management of patients with complex transfusion requirements (Grade 1C).

Transfusion in SCD requires careful consideration of both the haemoglobin concentration (Hb) and/or percentage of sickle haemoglobin (%HbS) in order to ensure maximal oxygen delivery to tissues without increasing overall blood viscosity to detrimental levels (Grade 1C).

A transfusion history should be obtained in all SCD patients requiring transfusion, whether elective or emergency. Close communication is essential between clinical

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and laboratory teams so that appropriate blood is given (Grade 1C).

Individuals with SCD are high-risk surgical patients. Close liaison between all clinical teams is essential with preoperative optimisation and appropriate postoperative care, whether transfused or not (Grade 1C).

Virology testing [hepatitis B, hepatitis C and human immunodeficiency virus (HIV)] should be undertaken at presentation and hepatitis B vaccination should be given to all patients with SCD, irrespective of previous or prospective planned transfusions. SCD patients on regular transfusions should be screened annually for hepatitis B, hepatitis C and HIV (Grade 1C).

The choice of transfusion method, i.e., simple (top up) or exchange, should be based on clinical judgement of individual cases, taking into account the indication for transfusion, the need to avoid hyperviscosity and minimise alloimmunisation, maintenance of iron balance, venous access issues and available resources (Grade 1C).

All hospitals that are likely to admit SCD patients should have staff trained in manual exchange procedures and clearly identified manual exchange procedures, as this can be lifesaving in emergency situations (Grade 1C).

Large referral centres managing patients with SCD should have facilities and trained staff for automated exchange transfusion (Grade 1C).

If transfusion is needed, patients with SCD should be given ABO-compatible, extended Rh- and Kell-matched units. If there are clinically significant red cell antibodies (current or historical) then the red cells selected should be negative for the corresponding antigens (Grade 1C).

Patients with SCD must also have extended red blood cell (RBC) antigen typing performed, which may assist with further serological testing and selection of red cell units if there are haemolytic reactions and complex transfusion requirements (Grade 1C).

Blood provided for SCD patients should be HbS negative and, where possible, should be <10 days old for simple transfusion and <7 days old for exchange transfusion but older blood may be given if the presence of red cell antibodies makes the provision of blood difficult (Grade 1C).

All patients with SCD should carry a transfusion card indicating that they have 'special requirement' and, in particular, giving information of any alloantibody (Grade 2C).

Patients with multiple red cell alloantibodies or antibodies to rare antigens need a clear agreed plan given that blood may be difficult to source in the elective or emergency setting. Close liaison between all clinical teams, the hospital transfusion laboratory and the national blood service is essential to ensure appropriate provision of blood (Grade 1C).

All clinicians managing patients with SCD should be aware of the risk of haemolytic transfusion reactions to ensure prompt recognition and management. Close liaison is needed with haemoglobinopathy specialists and blood services for investigation and management (Grade 1C).

Any adverse events or reactions related to transfusion should be appropriately investigated and reported to local risk management systems and to UK Haemovigilance Schemes (Grade 1C).

Goals of transfusion in SCD

Red cell (RBC) transfusion in SCD may be necessary in the management of acute complications or electively to prevent the development or progression of chronic complications. In both settings, transfusion may be administered by simple (top up) transfusion or by exchange transfusion (where patient red cells are removed and replaced with donor red cells). Exchange transfusion can be performed manually (Porter & Huehns, 1987) or with an automated cell separator (Janes *et al*, 1997; Lawson *et al*, 1999; Kuo *et al*, 2015; Tsitsikas *et al*, 2016) (see section Exchange transfusion techniques).

The major goals of transfusion in SCD are (i) improving oxygen-carrying capacity by correcting anaemia and (ii) preventing or reversing complications of SCD related to vaso-occlusion and haemolysis (by decreasing the proportion of HbS in relation to HbA).

General principles of practice

Seeking specialist help and advice

Sickle cell disease patients are at risk of haemolytic transfusion reactions due to increased rates of alloimmunisation (Rosse *et al*, 1990; Vichinsky *et al*, 1990). Poor communication may contribute to the failure to meet special transfusion requirements because these patients tend to be transfused out of hours, or at hospitals where their previous history is unknown (Vichinsky, 2012; Bolton-Maggs & Cohen, 2013; O'Suoji *et al*, 2013). Co-existing morbidities increase susceptibility to circulatory overload and the requirement for phenotyped blood can pose logistical difficulties (Flickinger, 2006). Expert haematology advice must be sought before a decision is made to transfuse, unless in an emergency, such as life-threatening acute blood loss. Complex patients should be discussed with consultants in specialist haemoglobinopathy teams and the national blood service.

Recommendation

The decision to transfuse or exchange transfuse an adult or paediatric patient with sickle cell disease (SCD) needs the input of a clinician with appropriate experience and specialist advice should be obtained for the management of patients with complex transfusion requirements (Grade 1C).

Clinical significance of steady state values

Steady state Hb varies between genotypes and between individuals with the same genotype (Serjeant & Serjeant 2001). Typical values are 60–90 g/l in SS, 70–90 g/l in S/β^o thalassaemia, 90–120 g/l in S/β^+ thalassaemia and 90–140 g/l in SC (National Heart, Lung, and Blood Institute [NHLBI] 2014). It is important to remember that some patients with SS have steady state Hb concentrations of up to 130 g/l or higher (Serjeant & Serjeant, 2001). It should be noted that, because of the low oxygen affinity of haemoglobin S, the steady state Hb is appropriate to the individual and is not in itself an indication for transfusion.

Each patient's baseline Hb and reticulocyte count should be documented in their clinical record. Changes in reticulocyte level reflect amounts of haemolysis and red cell production, which may be helpful in identifying the cause of worsening anaemia. An acute drop in Hb by >20 g/l from steady state should prompt a review for the aetiology and the need for transfusion (NHLBI, 2014) but may be tolerated in the absence of additional pathologies such as cardiovascular instability or hypoxia. (Serjeant, 2003). A chronic, progressive decrease in Hb should also prompt further investigation.

Recommendation

The decision to transfuse a patient with SCD, whether for worsening anaemia or for complications of SCD, must take into account the degree of anaemia relative to the patient's steady state haemoglobin concentration and overall clinical condition (Grade 1C).

Post-transfusion haemoglobin and %HbS and avoidance of hyperviscosity

Complications from sickling are related to the proportion of red cells containing HbS (%HbS) (or HbS+C in SC). These risks may be minimised by reducing the %HbS through transfusion, but no single %HbS target covers all indications. Randomised controlled studies have shown a transfusion target of HbS ≤30% (compared with no transfusion) is effective in reducing incidence rates of stroke (Adams *et al*, 1998; Adams & Brambilla, 2005; DeBaun *et al*, 2014), vaso-occlusive crises, acute chest syndrome, priapism and new symptomatic avascular necrosis (DeBaun *et al*, 2014). However, other randomised trials have shown higher targets of <35% and<50% reduced pain rates in prophylactically transfused pregnant women (Koshy *et al*, 1988) and perioperative complications in surgical patients transfused preoperatively (Howard *et al*, 2013), respectively. Some observational studies used %HbS targets of 25–40% in acute chest syndrome (Maitre *et al*, 2000; Lombardo *et al*, 2003; Velasquez *et al*, 2009).

The post-transfusion %HbS target depends on several factors, including the indication, the patient's background sickle history, severity of the acute illness, organ dysfunction, and clinical response to the initial transfusion. As a pragmatic approach, a target of HbS <30% is recommended in acute syndromes, such as severe acute chest syndrome, acute stroke and multi-organ failure syndrome (Swerdlow, 2006), and in patients receiving long-term transfusions for prevention of problems, such as stroke (Wang *et al*, 1991; Pegelow *et al*, 1995; Adams *et al*, 1998; Adams & Brambilla, 2005; DeBaun *et al*, 2014). In very sick patients, a lower %HbS may be desirable. In acute anaemia, it is usually sufficient to give a simple transfusion back to the steady state Hb (Telen, 2001) rather than use a %HbS target. Specialist advice should be sought for individual cases.

Hyperviscosity is a potential problem and any decrements in %HbS must be achieved without increasing the haematocrit unduly. Serious adverse events, including death, have been reported from over-transfusion (Royal & Seeler, 1978; Serjeant, 2003; Raj *et al*, 2013). The patient's baseline Hb, transfusion status and %HbS should be taken into account when determining the target post-transfusion Hb in any given situation. In SS patients with baseline Hb <90 g/l who are not on chronic transfusions, the post-transfusion Hb should not exceed 100 or 10–20 g/l above baseline, particularly if the post-transfusion %HbS exceeds 30% (see section Hyperviscosity). Care should be taken not to exceed baseline Hb values for sickle cell patients with high steady state Hb (>100 g/l).

For chronically transfused patients, the post-transfusion Hb may be set at a higher level if the pre-transfusion HbS is low; in these circumstances, the patient has a higher percentage of normal affinity haemoglobin A, and the risk of hyperviscosity is consequently lower. For these patients, the post-transfusion Hb should be decided on an individual basis and will depend on the %HbS.

Recommendations

In patients with sickle cell anaemia, transfusion to HbS <30% will prevent or reverse most acute sickle complications and significantly reduce long-term complications in chronically transfused patients.

Baseline Hb and % HbS should be taken into consideration in setting the target post-transfusion Hb in order to avoid hyperviscosity. In sickle cell anaemia patients with baseline Hb <90 g/l and not on regular transfusions, the post-transfusion Hb should not exceed 100 g/l, particularly if %HbS is greater than 30%. The post-transfusion Hb can be set at a higher target in chronically transfused patients or if %HbS is low, but should be individualised to each patient. Patients with high baseline Hb (>100 g/l) should not be transfused above their steady state Hb (Grade 1C).

Transfusing acutely ill patients

Acutely ill SCD patients may deteriorate rapidly so transfusion issues should be considered early, including any recent

transfusions, previous haemolytic transfusion reactions, and alloantibody formation. Baseline investigations should include: full blood count, reticulocyte count, and blood group with antibody screen. The transfusion request form must clearly state that the patient has SCD so that special transfusion requirements are met.

For patients presenting to a different hospital from usual, their primary hospital should be contacted for their baseline Hb, reticulocyte count, transfusion history, red cell phenotype/genotype and history of alloantibodies. The patient may have a card bearing details of their phenotype and/or alloantibodies.

Red cell units usually have to be ordered from the National Blood Service and this may introduce delay, especially for individuals with alloantibodies.

Meticulous attention should be paid to all aspects of SCD management, particularly adequate analgesia, hydration and incentive spirometry, to help prevent the development of critical organ complications for which transfusion may be required.

Recommendation

A transfusion history should be obtained in all SCD patients requiring transfusion, whether elective or emergency. This includes details of the patient's red cell phenotype and any red cell antibodies (current and historical). Hospitals should have robust systems in place to enable transfusion laboratories to clearly identify samples for sickle cell patients. Close communication is essential between clinical and laboratory teams so that appropriate blood is given (Grade 1C).

Monitoring patients for long-term transfusion complications

Transfusion has risks of alloimmunisation, iron overload and transfusion-transmitted infections.

Alloimmunisation can cause major difficulties (Vichinsky, 2001) (see section Patients with complex transfusion requirements) and early review should be undertaken with consideration of alternative treatments, such as hydroxycarbamide.

It is essential that both intermittently and regularly transfused patients are monitored for iron overload and treated accordingly (NHLBI, 2014). Ferritin is an unreliable marker of iron overload as it remains elevated for weeks after a painful crisis (Porter & Huehns, 1987). Furthermore, changes in ferritin with chelation therapy may be absent even when changes in hepatic iron levels are significant (Vichinsky *et al*, 2007). Therefore assessment of liver iron concentration using validated non-invasive magnetic resonance imaging techniques is recommended for patients with suspected or documented transfusional iron overload; a testing frequency of every 1–2 years has been suggested (NHLBI, 2014).

Transfusion-transmitted infections may occur, though the risk is currently very low in the UK (Watkins *et al*, 2012). All SCD patients should be immunised against hepatitis B whether or not they are on regular transfusions (Sickle Cell Society, 2008) and annual testing should be undertaken for transfusion-transmitted viruses if transfused.

Recommendation

Chronically transfused SCD patients should be regularly monitored for iron overload with serum ferritin at least every 3 months; liver iron measurements should be performed every 1–2 years for those with suspected or proven iron overload. Intermittently transfused patients should also be monitored for iron overload as part of their routine care (Grade 1C).

Virology testing [hepatitis B, hepatitis C and human immunodeficiency virus (HIV)] should be undertaken at presentation and hepatitis B vaccination should be given to all patients with SCD irrespective of previous or prospective planned transfusions. SCD patients on regular transfusions should be screened annually for hepatitis B, hepatitis C and HIV (Grade 1C).

Considerations in choosing simple (top up) or exchange transfusion

Factors that are important when deciding between simple or exchange transfusion are outlined below.

Indication for the transfusion

Simple transfusion is preferable when the primary reason for the transfusion is to prevent or reverse the effects of severe anaemia (e.g. aplastic crisis). Exchange transfusion allows the removal of sickle cells and their replacement by normal red cells and is the preferred option where an immediate or sustained reduction in complications of SCD is required without an undesirable increase in blood viscosity (e.g. severe acute chest syndrome).

Hyperviscosity

The viscosity of sickle red cells is much higher than that of normal red cells, and the risk of hyperviscosity at a given Hb is dependent on the %HbS and the haematocrit (Anderson *et al*, 1963; Chien *et al*, 1970; Schmalzer *et al*, 1987; Alexy *et al*, 2006). Increased viscosity compromises oxygen delivery and exacerbates the sickling process (Schmalzer *et al*, 1987; Ballas & Mohandas, 2004).

The viscosity effect of sickle red cells is reduced but not eliminated by the presence of normal red cells (Swerdlow, 2006). Simple transfusion leads to a rise in haematocrit, and any increment in oxygen carrying capacity is offset by increased blood viscosity (Schmalzer *et al*, 1987; Wayne *et al*,

1993; Alexy *et al*, 2006). Exchange transfusion removes HbS-containing cells and decreases blood viscosity (Schmalzer *et al*, 1987).

When the pre-transfusion Hb is close to steady state or is high for other reasons (such as SC) exchange transfusion is preferred. Normal red cells support maximum oxygen transport at Hb 140–160 g/l, but in untransfused sickle cell anaemia patients, it is lower at 100–110 g/l because of the higher viscosity of sickle red cells (Swerdlow, 2006). In such patients, it is unwise to exceed a post-transfusion Hb target of 100–110 g/l, without an accompanying reduction in % HbS to less than 30% (see section Post-transfusion haemoglobin and %HbS and avoidance of hyperviscosity).

Iron balance

The rate of iron accumulation depends on the type of transfusion used (simple *versus* exchange) (Porter & Garbowski, 2013). Simple transfusion inevitably causes greater positive iron balance than exchange transfusion (Cohen *et al*, 1992; Kim *et al*, 1994; Adams *et al*, 1996; Hilliard *et al*, 1998; Harmatz *et al*, 2000; Olivieri, 2001; Brown *et al*, 2009). Iron accumulation in exchange transfusion depends on the difference between the numbers of red cells removed and those given and is influenced by the type of exchange (manual or automated), as well as Hb and %HbS values pre- and post-exchange transfusion (Porter & Garbowski, 2013). Chronic manual exchange transfusions may decrease the rate of iron loading by approximately 40% relative to simple transfusion (Porter & Huehns, 1987) but automated exchanges can achieve neutral or even negative iron balance (Kim *et al*, 1994).

Alloimmunisation

The rate of alloimmunisation in SCD is dependent on a number of factors including the number of units transfused (Rosse *et al*, 1990; Vichinsky *et al*, 1995). Automated exchange transfusion programmes consume more red cell units than chronic partial exchange or simple transfusion procedures (Hilliard *et al*, 1998). However, a retrospective study of children on chronic transfusions reported a significantly lower rate of alloimmunisation for those on automated apheresis compared to children on simple transfusions even though blood consumption was significantly higher in the erythrocytapheresis group (Wahl *et al*, 2012). Concerns about increased alloimmunisation with exchange transfusion may be unjustified and erythrocytapheresis should not be withheld from those likely to benefit from it.

Venous access

Venous access is a problem in a substantial number of adult patients with SCD and may be particularly problematic for automated exchange where good vascular access is essential to maintain flow rates. Manual exchange can be performed using a single line, but it is slow. It can only be performed isovolaemically using two lines in a two-arm technique. Automated and manual exchange can be performed using peripheral cannulae, but short term femoral line insertion may be required (Billard *et al*, 2013).

Indwelling central venous catheters have a high complication rate, particularly infection, among SCD patients compared with other patient groups (McCready *et al*, 1996; Jeng *et al*, 2002; Wagner *et al*, 2004; Alkindi *et al*, 2012; Shah *et al*, 2012). Lower complication rates have been reported in one small study in children (Bartram *et al*, 2011) and in another study where a particular implantable device was used (Raj *et al*, 2005). Dual lumen ports may be considered for chronic automated exchanges but there is limited data regarding their long-term use.

Resources

More resources are required for exchange transfusion than simple transfusion especially in relation to staffing and equipment. Chronic automated exchange programmes are much more expensive than simple transfusion programmes but the increased costs may be offset by fewer hospital visits and reduced requirement for iron chelation therapy (Hilliard *et al*, 1998).

Recommendation

The choice of transfusion method, simple or exchange, should be based on clinical judgement of individual cases, taking in account the indication for transfusion and the need to avoid hyperviscosity and minimise alloimmunisation, maintenance of iron balance and venous access issues. Automated exchange should be available to all patients and not be limited by resources (Grade 1C).

Exchange transfusion techniques

Both manual and automated exchange transfusions are suitable in the emergency setting for inpatients with acute sickle complications (Janes *et al*, 1997; Vichinsky *et al*, 2000; Velasquez *et al*, 2009) as well in the outpatient setting for elective indications (Vichinsky *et al*, 1995; Adams *et al*, 1998; Singer *et al*, 1999; Raj *et al*, 2005; Billard *et al*, 2013). The volume of blood exchanged and the target final Hb can be adjusted. The ability of these two methods to achieve pre-defined haematological targets, rate of complications, blood usage and clinical outcome over a 1-year period were compared in a retrospective observational cohort study (Kuo *et al*, 2015).

Automated red cell exchange

This has advantages over manual red cell exchange and is the preferred technique where available. It reduces %HbS faster

than manual exchange because plasma, platelets and white cells are returned to the patient (Lawson *et al*, 1999). The procedure takes around 2 h with good venous access (Kim *et al*, 1994; Janes *et al*, 1997; Lawson *et al*, 1999) and is well tolerated (Lawson *et al*, 1999). Additionally, its effectiveness in reducing %HbS allows up to 6-weekly transfusion intervals (Kalff *et al*, 2010). It also limits or eliminates iron accumulation (Kim *et al*, 1994). Automated red cell exchange is suitable for both children (Singer *et al*, 1999; Velasquez *et al*, 2009; Billard *et al*, 2013) and adults (Janes *et al*, 1997; Lawson *et al*, 1999; Kozanoglu *et al*, 2007; Kalff *et al*, 2010).

Hypocalcaemia may occur and increases with the number of units of blood transfused, but is easily prevented by the intravenous administration of calcium during the procedure (Lawson *et al*, 1999). Dilutional thrombocytopenia may also occur (Tsitsikas *et al*, 2016).

Fluid shifts occur during apheresis so hydration status should be addressed pre-procedure; anti-hypertensive medications and diuretics may need to be withheld. Apheresis machines pool a fixed volume of blood *ex vivo* and where this is >15% of the patient's total blood volume, priming the machine with donor blood prior to apheresis may be useful. This approach may also be used for patients who have Hb >20% below their steady state Hb; alternatively, simple transfusion could be given prior to apheresis.

Venous access can be a challenge in order to achieve adequate flow rates and femoral access may be required. For chronic automated apheresis, some centres use indwelling double lumen Vortex® ports (AngioDynamics, Latham, NY, USA), but these require special attention because of the risks of infection and thrombosis. These should be used only when other approaches are not possible.

The availability of cell separators and/or trained operators for automated red cell exchange in SCD is limited nationally so trained staff may not be available outside normal working hours. Manual exchange transfusions may be more practical in these circumstances and is more widely available. In view of its advantages over manual exchange transfusion, we recommend that all patients with SCD should have access to automated exchange transfusion at a specialist centre. The advantages of automated exchange transfusion have been recognised in a recent medical technology guidance published by the National Institute for Health and Care Excellence (NICE, 2016). NICE has recommended the use of the Spectra Optia Apheresis System (Terumo BCT, Lakewood, CO, USA) for automated red cell exchange in the treatment of sickle cell patients who require regular transfusions (NICE, 2016).

Manual red cell exchange

A manual red cell exchange typically aims to exchange about one-third of the patient's blood volume thereby achieving about 30% HbA. This should be done isovolaemically, typically removing a larger volume of blood than that transfused and making up the volume difference with 0·9% sodium chloride (normal saline). Although practices vary, a typical adult exchange would involve the removal of 4 red cell units with transfusion of 3 units; this will increase the Hb by 10–20 g/l and may require the removal of additional units at the end of the procedure (Porter & Huehns, 1987). This takes several hours and may need repeating to achieve the desired transfusion targets. Manual exchanges can be performed in any ward or day unit setting but requires the operator to have familiarity with the procedure. In view of its simplicity and effectiveness in reversing the acute complications of SCD, it is imperative that all hospitals likely to admit SCD patients have trained staff to perform the procedure in an emergency or, as a minimum, have a written protocol that is easy to follow. We recommend that manual red cell exchange transfusion be a requirement of specialist haematology training.

Recommendations

All hospitals that are likely to admit SCD patients should have staff trained in manual exchange procedures and clearly identified manual exchange protocols, as this can be lifesaving in emergency situations (Grade 1C).

Automated exchange transfusion should be available at all specialist centres and all patients with SCD should have access to it (Grade 1C).

Laboratory aspects

Alloimmunisation in SCD

Alloimmunisation is common in SCD (Yazdanbakhsh *et al*, 2012), resulting in an increased frequency of haemolytic reactions (Bolton-Maggs & Cohen, 2013). Significant differences in RBC antigen frequencies between Caucasian donors and African and Afro-Caribbean recipients contribute to increased rates of alloimmunisation (Vichinsky *et al*, 1990). The use of Rh- and K- matched units has reduced alloimmunisation and haemolytic transfusion reactions, but sensitisation continues against Rh variants that are identifiable on molecular genotyping but not by serological methods (Lasalle-Williams *et al*, 2011; Noizat-Pirenne & Tournamille, 2011; Chou *et al*, 2013; Miller *et al*, 2013; O'Suoji *et al*, 2013).

Following alloimmunisation a rapid reduction in alloantibody titre means it may become undetectable by routine antibody screening (Rosse *et al*, 1990), hence the need for accurate records.

Compatibility testing

Fully automated systems should be used for ABO typing to mitigate the risks of interpretation and transcription error. Antibody screening should always be part of pre-transfusion

testing. If an alloantibody is detected its specificity should be determined. If the patient is known to have formed a red cell alloantibody, each new sample should be fully tested to exclude the presence of further alloantibodies (Milkins *et al*, 2013). Samples should be sent to a red cell reference laboratory if there is difficulty in antibody identification or excluding clinically significant antibodies.

For patients not on a regular transfusion programme, it is recommended that antibody screening be repeated after every episode of transfusion to document whether or not any new antibodies have formed (Milner *et al*, 1985).

Serological studies should be performed using blood collected no more than 72 h in advance of the transfusion when the patient has been recently transfused (Milkins *et al*, 2013). The pre-transfusion sample should be available for at least 3 days after transfusion to allow repeat ABO grouping in the event of an acute transfusion reaction. Keeping patient plasma for 7–14 days after transfusion may be useful for investigation of delayed transfusion reactions (Milkins *et al*, 2013).

Extended red cell phenotype/genotype – serological and molecular

An extended phenotype (or genotype) including C, c, E, e, K, k, Jka, Jkb, Fya, Fyb, S, s should be performed on all patients at baseline. If the patient is S- s-, then U typing should be performed (Milkins *et al*, 2013). If the patient has not been transfused within 3 months then this can be undertaken serologically, otherwise the genotype needs determination by molecular techniques (Chou & Westhoff, 2011; Milkins *et al*, 2013) through an appropriate reference laboratory. Except in extreme emergency, the patient's RBC phenotype should be known prior to transfusion (Milkins *et al*, 2013). The National Health Service Blood and Transplant (NHSBT) is currently undertaking a project (the Haemoglobinopathy Genotyping Initiative) to provide comprehensive extended RBC genotyping including RHD and RHCE variants on haemoglobinopathy patients.

Blood product selection

As a minimum, red cells should be matched for Rh (D, C, c, E, e) and K antigens (Vichinsky, 2001; Vichinsky *et al*, 2001; Milkins *et al*, 2013). Wherever possible, R_0 blood should be selected for patients who are typed as R_0 (Milkins *et al*, 2013). If R_0 blood is unavailable then rr blood can be used if urgent. Red cells should be HbS negative (Milkins *et al*, 2013).

If there are clinically significant red cell antibodies (current or historical) then the red cells selected should be negative for the corresponding antigens. Red cells should be less than 10 days old for simple transfusion and, if possible, <7 days old for exchange transfusion. This may not be possible in multiply alloimmunised individuals for whom the freshest units available should be used (Milkins *et al*, 2013). Unexplained haemolytic reactions may be due to atypical Rh phenotypes in SCD recipients who type as positive for Rh antigens but mount an immune response to apparently Rh-compatible blood (Chou *et al*, 2013).

Documentation of phenotype and alloantibodies

All sickle cell patients should be issued with a laminated card bearing their full red cell phenotype and, in particular, information as to whether they have formed an antibody. Clear instructions must be given to the patient as to how to use the card (Vichinsky, 2012).

National databases can greatly facilitate communication of phenotypes and alloantibodies between laboratories For example, NHSBT, the National Blood Service in England, is now implementing 'Specialist Services Electronic Reporting using the Sunquest ICE Web Browser' (Sp-ICE) for Red Cell Immunohaematology (RCI) allowing ready access to its serology results by hospitals (http://hospital.blood.co.uk/).

Recommendations

If transfusion is needed, patients with SCD must be given ABO-compatible, extended Rh- and Kell-matched units. If there are clinically significant red cell antibodies (current or historical) then the red cells selected should be negative for the corresponding antigens (Grade 1C).

Patients with SCD must also have extended RBC antigen typing performed, which may assist with further serological testing and selection of red cell units if haemolytic reactions occur or there are complex transfusion requirements (Grade 1C).

Blood provided for SCD patients should be HbS negative and, where possible, be <10 days old for simple transfusion and <7 days old for exchange transfusion, but older blood may be given if the presence of red cell antibodies makes the provision of blood difficult (Grade 1C).

All patients with SCD should carry a transfusion card indicating they have 'special requirement' and, in particular, information as to whether they have formed an antibody (Grade 2C).

Patients with complex transfusion requirements

Multiple antibody combinations or antibodies to rare antigens not seen in Caucasian donors (e.g. Fy^{a-b-}) can cause difficulty in sourcing blood. The development of anti-U and anti-Js^b can be particularly challenging (Poole, 2002). Alloimmunisation to Rh antigens is further complicated by genetic diversity in this blood group system in people of African origin (Pham *et al*, 2011; Kappler-Gratias *et al*, 2014). The D, C or c and E or e are encoded by two homologous genes, namely *RHD* and *RHCE*. Variant *RHD* and

RHCE alleles resulting in altered D, C and e antigens can result in alloimmunisation in these patients but the clinical picture can be challenging. The patients appear to have autoantibodies because standard serological testing types them as positive for the corresponding antigen. However, molecular testing will demonstrate the relevant variant antigen therefore highlighting that the antibody is an alloantibody (Sippert *et al*, 2015). Accordingly, high-resolution RH genotyping may be required to identify this situation and make provision of antigen-negative red cells feasible (Chou *et al*, 2013).

Red cell alloimmunisation increases clinical risk due to delays in securing compatible units, as well as increased potential for delayed haemolytic transfusion reactions. Careful planning and communication between all teams is essential; this includes liaising with the Blood Service for sourcing rare blood from donors and providing frozen units where necessary.

Management of patients requiring rare blood

The principal aims are to provide compatible blood in a timely manner and to minimise the risks from transfusion.

Patients who are difficult to transfuse should have a written plan detailing: the transfusion requirements, a contingency plan for emergency transfusion, the contact details of the patient's sickle/haematology consultant and a recommendation to involve a National Blood Service reference laboratory.

In England, NHSBT provides hospital transfusion laboratories access to **Sp**ecialist Services Electronic Reporting System, delivered via Sunquest **ICE** (Sp-ICE) for review of patient's serological records (http://hospital.blood.co.uk/diagnostic-services/sp-ice-browser/www.hospital.blood.co.uk).

For long-term management, hydroxycarbamide can reduce the need for transfusions and should be considered (Charache *et al*, 1995).

Recommendations

Patients with multiple red cell alloantibodies or antibodies to rare antigens need a clear agreed plan because blood may be difficult to source in the elective or emergency setting. Close liaison between all clinical teams, the hospital transfusion laboratory and the National Blood Service is essential to ensure appropriate provision of blood (Grade 1C).

Haemolytic transfusion reactions

Sickle cell patients are at increased risk of haemolytic transfusion reactions due to a high rate of red cell alloimmunisation, previous red cell antibodies that are currently undetectable, increased likelihood of urgent transfusion out of hours and transfusion in multiple different hospitals.

Two main patterns of delayed haemolytic transfusion reactions (DHTR) occur in SCD patients. Most reported cases are classical DHTR, which are associated with the formation of new alloantibodies, a positive direct antiglobulin test (DAT) and shortened survival of the transfused red cells (Noizat-Pirenne, 2012). The second type of DHTR is a syndrome in which hyperhaemolysis (defined as the destruction of both transfused and autologous red cells) results in often profound and life-threatening anaemia often without demonstrable new antibodies (Petz *et al*, 1997; Win, 2009).

Classical delayed haemolytic transfusion reaction

These reactions are due to anamnestic immune responses in alloimmunised patients and are common in SCD, occurring in 4–11% of transfused patients (Wanko & Telen, 2005). Patients present with a triad of fever, jaundice and anaemia, most commonly 7–10 days after transfusion, which may be accompanied by sickling pain. There is clear laboratory evidence of haemolysis and shortened survival of the transfused red cells (with a fall in %HbA), a positive DAT and new alloantibodies identified in the patient's plasma or red cell eluate. Reticulocytosis is a common finding. The key steps in the approach to the investigation of a possible haemolytic transfusion reaction are summarised in Table I.

Alloantibody identification may require the services of a red cell reference laboratory. If the identity of the new alloantibody cannot be determined and further transfusion is required, the provision of extended antigen matched blood should be considered, however, transfusion should be avoided unless anaemia is severe.

Hyperhaemolysis syndrome

Hyperhaemolysis is a subtype of delayed haemolytic transfusion reaction which can potentially cause life-threatening acute anaemia (King *et al*, 1997; Petz *et al*, 1997; Aygun *et al*, 2002; Talano *et al*, 2003; Win, 2009; de Montalembert *et al*, 2011; Danaee *et al*, 2015). Five cases with SCD were reported to Serious Hazards of Transfusion (SHOT) in 2011 (Bolton-Maggs & Cohen, 2012) and three in 2012 (Bolton-Maggs *et al*, 2013). The first fatal case of hyperhaemolysis in the UK was reported in 2010 (Knowles & Cohen, 2011).

The characteristic presenting features are severe sickle pain, fever and haemoglobinuria (Petz *et al*, 1997; Talano *et al*, 2003; Win, 2009; de Montalembert *et al*, 2011).

There is severe destruction of both donor and autologous red cells (King *et al*, 1997; Petz *et al*, 1997; Talano *et al*, 2003; de Montalembert *et al*, 2011). Laboratory features include:

- Post-transfusion Hb is lower than before transfusion (Petz *et al*, 1997).
- %HbA decreases or becomes absent (King *et al*, 1997).

Table I. Investigation of a haemolytic transfusion reaction.

(1) Document evidence of haemolysis.
- Check haemoglobin concentration and review blood film
- Check bilirubin, lactate dehydrogenase and reticulocyte count
- Check urine for haemoglobinuria and if positive and hyperhaemolysis suspected, consider serial high performance liquid chromatography analysis of the urine

(2) Serological testing on pre-transfusion and post-transfusion blood samples.
- Repeat ABO/Rh D typing
- Check antibody screen on both samples
- Red cell units transfused within 12–24 h should be crossmatched against both the pre- and post-reaction samples
- Check the direct antiglobulin test (DAT). A positive DAT may be encountered as part of an investigation

(3) If antibody screen positive
- Determine the specificity of the antibody (ies) – (antibody investigations may demonstrate a new alloantibody or antibodies in a patient with a delayed haemolytic transfusion reaction)
- If the specificity of the red cell antibody is not clearly determined the sample should be sent to a red cell reference laboratory

(4) If DAT positive
- Prepare an eluate to test for the presence of specific alloantibodies
- Even if no new red cell alloantibody is detected in post-transfusion sample as above, but DAT is positive, red cell eluate studies should be undertaken

(5) Selection of red cell units for further transfusion
- Carefully consider the need for further transfusion with consultant input and discussion with the National Blood Service if complex transfusion requirements
- Select ABO extended Rh and K matched units negative for the relevant antigen(s) to which there are current or historical antibodies
- Undertake serological crossmatch to check compatibility; **electronic issue should not be used**
- If the identity of the new alloantibody is in doubt despite further specialist testing, consider providing extended antigen matched blood (if serological phenotyping cannot be used because of the presence of transfused donor red blood cells, the sample should be sent to an appropriate reference laboratory for molecular red cell genotyping)

- HbS and HbA are present on serial analysis of urine by high performance liquid chromatography (Win *et al*, 2001).
- A fall in the absolute reticulocyte count (from patient's usual level) (Petz *et al*, 1997; Talano *et al*, 2003; Win, 2009).

Serum ferritin (a non-specific marker for macrophage activation) correlates well with disease activity and clinical response (Win *et al*, 2012).

The DAT is often negative and new red cell alloantibodies are frequently not detected on serological investigation. New alloantibodies are usually identified in DAT positive cases, although their appearance may be delayed (Garratty, 1997; Talano *et al*, 2003; Win *et al*, 2008).

Additional transfusion, even with antigen-matched crossmatch-compatible units, may lead to further haemolysis and a protracted course or even death (Milner *et al*, 1985; Petz *et al*, 1997) but must not be withheld in patients with life-threatening anaemia.

Management depends upon the severity of anaemia and speed of haemolysis. In mild cases further transfusion should be avoided. In severe cases, early administration of intravenous immunoglobulin (IVIG) and steroids may correct the anaemia and resolve haemolysis (Win *et al*, 2001, 2004, 2008, 2010; Danaee *et al*, 2015). Additional doses of IVIG and methylprednisolone may occasionally be required (Danaee *et al*, 2015). In rapid severe haemolysis, further transfusion may be required to prevent death from anaemia; this should be given with IVIG and steroid cover (Danaee *et al*, 2015).

Hyperhaemolysis may also recur after recovery if subsequent transfusion is given, even after several years, but this is unpredictable (Win, 2009). Recurrence of hyperhaemolysis may be prevented by the administration of IVIG and methylprednisolone prior to subsequent transfusions (Danaee *et al*, 2015).

Erythropoietin (Talano *et al*, 2003; de Montalembert *et al*, 2011), rituximab (Noizat-Pirenne *et al*, 2007; Bachmeyer *et al*, 2010) and eculizumab (Dumas *et al*, 2016) have been used in hyperhaemolysis but further evaluation is required to substantiate their role. A small observational study on alloimmunised sickle cell patients with a history of severe DHTR has suggested that rituximab may potentially minimise the risk of further alloimmunisation and severe DHTR, but does not prevent haemolysis in all patients (Noizat-Pirenne *et al*, 2015). Informed consent should be obtained from the patient before rituximab is used (Win, 2013).

Autoimmune haemolytic anaemia

Autoantibody formation (usually auto-anti e) is more common in multiply alloimmunised SCD patients and has a

reported incidence of 6–10% (Castellino *et al*, 1999; Noizat-Pirenne, 2012). Autoantibodies can mask the presence of alloantibodies and sometimes cause clinically significant haemolysis (Chaplin & Zarkowsky, 1981; Castellino *et al*, 1999; Aygun *et al*, 2002; Noizat-Pirenne *et al*, 2007). Most cases respond to corticosteroid therapy (Chaplin & Zarkowsky, 1981; Castellino *et al*, 1999).

With the increasing availability and application of molecular Rh typing, it is becoming clear that many supposed autoantibodies are in fact Rh alloantibodies due to variant RH alleles that are capable of causing haemolytic reactions (Sippert *et al*, 2015).

Recommendations

All clinicians managing patients with SCD must be aware of the risk of haemolytic transfusion reactions to ensure prompt recognition and management. Close liaison is needed with haemoglobinopathy specialists and blood services for investigation and management (Grade 1C).

Any adverse events or reactions related to transfusion should be appropriately investigated and reported to local risk management systems and to National Haemovigilance Schemes (Grade 1C).

Date for guideline review

This guideline will be reviewed within 5 years of completion of the final draft.

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Conflict of interest

None of the authors have declared a conflict of interest.

Disclaimer

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