Sickle cell disease: when and how to transfuse

Jo Howard

Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; and King's College London, United Kingdom

Blood transfusion remains an important therapeutic intervention in patients with sickle cell disease (SCD), aiming to both increase the oxygen carrying capacity of blood and to reduce the complications of vaso-occlusion. Simple, manual exchange and automated exchange can be effective in reducing the acute and chronic complications of SCD, and the advantages and disadvantages of each methodology mean they all have a role in different situations. Evidence for the role of emergency transfusion in the management of the acute complications of SCD, including acute pain and acute chest syndrome, comes from observational data. Several important randomized controlled trials have shown the efficacy of transfusion in primary and secondary stroke prevention in patients with SCD but, outside these areas, clinical practice lacks a clear evidence base. Evidence for the role of long-term transfusion in the prevention of the non-neurologic chronic complications of SCD comes from analysis of secondary outcomes of these randomized trials and from observational data. In view of the paucity of data, the risks and benefits of transfusion should be fully discussed with patients/families before a long-term transfusion program is commenced. Evidence is only available for the role of preoperative transfusion or for prophylactic transfusion through pregnancy in certain situations, and the role of transfusions outside these situations is discussed. Questions about when and how to transfuse in SCD remain and will need further randomized trials to provide answers.

Learning Objectives

- To describe the advantages and disadvantages of simple, manual exchange and automated exchange transfusion
- To discuss when transfusion should be used to treat the acute and chronic complications of sickle cell disease
- To discuss the role of preoperative transfusion and of transfusion during pregnancy in decreasing sickle-related complications

Introduction

The mainstay of treatment of patients with sickle cell disease (SCD) remains blood transfusion or hydroxyurea therapy. The use of blood transfusion in patients with SCD for the treatment of acute complications and as chronic long-term disease-modifying therapy is increasing over time, with total blood use increasing. Over a 10-year period, blood use in adults in a UK center increased from 1.7 to 3.86 units per patient per year, and rate of transfusion during acute admissions in children in the US increased from 14.2% to 28.8% ($P < .0001$).[1,2] This is in part caused by having an aging population with increasing medical comorbidities but is also a result of the improved safety of the blood supply and increasing evidence about the efficacy of blood transfusion in some clinical scenarios. Transfusion is not without risk, and in many parts of the world, patients do not have access to a safe and sustainable blood supply. Even in countries where blood is available and affordable, transfusion can be associated with complications including alloimmunization, iron overload, and infection.

Several key randomized controlled trials (RCTs) have shown the efficacy of chronic blood transfusion and hydroxyurea in primary and secondary stroke prevention in children and the lessons learned from these trials are embedded in practice.[3-7] Unfortunately, there is limited evidence for the role of transfusion in SCD outside these trials, and recommendation for transfusion is often based on observational data, expert opinion, or anecdote, which has led to great variation in practice. The recent Peer Review Program of services for patients with hemoglobin disorders in the UK (2014-2016), which reviewed 32 centers providing care for >7000 adults and 5000 children, found that rates of long-term transfusion at different centers vary between 0% and 42% for adults and between 1.2% to 19.5% for children (West Midlands Quality Review Service, www.wmqrs.nhs.uk, unpublished data) Indications for long-term transfusion show marked variation between centers, with comparisons between observational data in adults showing that the proportion of patients being transfused because of recurrent pain varies between 16% and 54%, because of stroke prevention varies between 8% and 66%, and for leg ulcers varies between 0% and 16%. Other indications for long-term transfusion include recurrent acute chest syndrome (ACS), priapism, pulmonary hypertension, renal dysfunction, and sickle hepatopathy.[1,8,9] This variation was confirmed among physicians in the US by a mail survey of transfusion practice.[10]

Although there is a paucity of randomized trials of transfusion outside the treatment of neurologic complications of SCD, we can use the secondary outcomes of the RCTs outlined here before to provide evidence for the efficacy (or not) of chronic transfusion therapy in the treatment of other chronic complications of SCD. These have been used in combination with prospective or retrospective observational

Conflict-of-interest disclosure: J.H. has consulted for Pfizer and Global Blood Therapeutics and has received honoraria from and has been affiliated with the Speakers Bureau for Novartis.

Off-label drug use: None disclosed.

data and evidence-based guidelines developed by experts to suggest when to transfuse patients with SCD.[11,12]

How to transfuse

Transfusions can be administered as a simple transfusion or as an exchange transfusion (Table 1). The aims of transfusion in SCD are both to increase oxygen-carrying capacity and to decrease the proportion of sickle hemoglobin (HbS) relative to hemoglobin A (HbA) to prevent or reverse the complications of vaso-occlusion. In the acute situation, simple transfusion will increase oxygen-carrying capacity but with a risk of hyperviscosity if the Hb is increased to significantly over the patient's baseline. Therefore, the target Hb should be 10 g/dL in patients with homozygous HbS (HbSS).[13] Exchange transfusion has the advantage of both increasing oxygen-carrying capacity and reducing HbS%. In patients on long-term transfusion, both repeated simple or exchange transfusion can maintain a low HbS%, and if HbS% is maintained below 30% to 40%, Hb can safely be maintained at a higher level with less risk of hyperviscosity. Simple transfusion is the most common method of transfusion used in chronic transfusion programs, particularly in children, but at the cost of high rates of iron loading. Most patients on long-term simple transfusion will need iron chelation therapy after approximately 1 year of transfusion, and lack of adherence to iron chelation will result in iron overload.

Exchange transfusions can be performed as a manual procedure or as an automated procedure using an apheresis machine. Manual exchanges are performed using repeated alternating isovolumetric phlebotomy and blood transfusion.[13,14] This can be a useful procedure, particularly in the acute situation to enable increase in Hb and oxygen-carrying capacity with concurrent removal of HbS-containing red cells to prevent hyperviscosity, but is time-consuming and needs skilled staff and constant medical supervision during the procedure. Suggested methodologies for manual exchange in adults and children are available.[13,15] Retrospective comparison of automated and manual exchange procedures in both adults and children have shown that automated procedures were more likely to achieve HbS% targets[8,16] and required half the time of manual procedures ($P < .0001$),[8] but alternative methodologies of manual exchange can achieve improved adherence with HbS% targets.[17,18] Control of iron loading with manual exchanges is intermediate between simple transfusions and automated exchanges.[14]

Automated red cell exchange (RCE) is well tolerated in patients with SCD and results in good control of S% without increase in viscosity. It is a rapid procedure, taking only 90 to 120 minutes, and can be performed in children as young as 5 years and as small as 20 kg. Its other main advantage is the decreased rate of iron loading associated with this procedure, with a reduction of iron loading of ~85% compared with simple transfusion. If used as the initial form of transfusion, it may prevent iron overload and can allow cessation of iron chelation in well-chelated patients.[19,20] A small proportion of patients (particularly those with a low baseline Hb level) will accumulate iron at a low rate even with RCE and may need concurrent iron chelation at a reduced intensity. Automated exchanges do require more blood than manual exchange or simple transfusion but are not associated with increased rates of alloimmunization.[8,19] The National Institute of Clinical Excellence has recently reviewed data on automated and manual exchange procedures and recommended automated RCE should be considered for patients who need regular transfusion, and it is cost-effective (www.nice.org.uk). Despite British recommendations that all patients with SCD should have access to automated RCE, recent peer review data in the UK (2015-2016) showed that several large sickle centers could not provide automated RCE.

Table 1. Comparison of transfusion methods

Simple transfusion	Manual exchange transfusion	Automated red cell exchange
Widespread availability	Widespread availability	Limited availability
Minimal staff training required	Some staff training required	Significant staff training required
Minimal specialist equipment	Minimal specialist equipment	Requires specialist equipment
Time-consuming for patient	Time-consuming for patient and staff	Rapid procedure
Risk of hyperviscosity with high Hb targets	Less risk of hyperviscosity	Less risk of hyperviscosity
Poor control of HbS%	Intermediate control of HbS%	Best control of HbS%
Short intervals between procedures	Intermediate intervals between procedures	Long intervals between procedures
High levels of iron accumulation	Intermediate levels of iron accumulation	Low levels of iron accumulation
Peripheral access is usual	Intermediate requirement for central access	High requirement for central access

Modification of the automated RCE procedure, preceding it by automated isovolumetric hemoreduction, may result in improved control of HbS%, decreased blood volume usage, and decreased iron loading, but this has not been subject to robust comparison.[21,22] Complications of acute hemoreduction may be seen in both the automated and manual setting and include hypovolemia (dizziness, syncope, headache, weakness) and a possible risk of acute neurologic complications caused by acute anemia. Symptoms of hypovolemia maybe reduced by administration of a normal saline bolus before the hemoreduction.

Obtaining robust venous access can be a problem in any patient on a long-term transfusion program, but is more problematic in patients on RCE because they need high rates of blood flow.[13,18] Patients may require temporary central venous access or permanent implantable devices, which have both been associated with increased rates of thrombosis or infection.

There are few clinical trials comparing simple and exchange transfusions. The decision for simple, manual, or automated exchange will depend on Hb level, clinical indication, and availability of automated technology. For patients about to embark on a long-term transfusion program, additional issues such as venous access, degree of prior iron loading, and availability of iron chelation must be considered and hence patient/family preferences are very important. In our service, freedom from iron chelation and the increased time period between transfusion mean that the majority of patients opt for automated RCE.

When to transfuse: transfusion for acute complications

Blood transfusion may be needed in the emergency situation for patients with SCD both to increase the oxygen-carrying capacity and to decrease vaso-occlusive complications (Table 2).[11,15] In the former, simple transfusion, if possible without causing an excessive increase in viscosity, may suffice, but if an urgent reduction in HbS% is required then an exchange transfusion will be preferred.[12]

Table 2. Summary of emergency indications for transfusion[11,15]

Indication	Comment
Acute anemia	Simple transfusion to baseline Hb
Acute ischemic stroke	Exchange transfusion
Acute pain	Not currently indicated unless additional complication
Acute chest syndrome	No transfusion, simple or exchange transfusion depending on severity
Acute priapism	Consider simple or exchange transfusion if no response to initial treatment
Multiorgan failure, acute sickle hepatopathy, severe sepsis	Exchange transfusion

Although there is little randomized trial evidence for the use of blood transfusion to treat many of the acute complications of SCD, there is extensive clinical experience, and clinical trials in many of these areas would no longer be ethical.

Acute anemia

Acute anemia is defined as a decrease in hemoglobin of >2 g/dL below baseline[11] and is often associated with symptomatic anemia. SCD presenting with acute anemia in a patient should be investigated for the cause (which includes rapid hemolysis, human erythrovirus [previously parvovirus], B19 infection, and splenic or hepatic sequestration) and, if symptomatic, should be treated with a simple transfusion aiming to return the hemoglobin to its baseline value. A single transfusion episode will usually suffice, but Hb should be monitored because a subsequent transfusion may be required to maintain Hb, and in sequestration syndromes, sequestered cells can return to the circulation, causing an increase in Hb and hyperviscosity.

Acute pain

The treatment of acute pain crisis is typically supportive with analgesia, fluids, and oxygen therapy. A pilot trial of red cell transfusion within 24 hours of admission with acute pain did not show a significant improvement in mean hospital stay (transfused vs nontransfused, 4.2 vs 5.8 days, $P = .44$), total opiate use (1.6 vs 4.2 mg/kg, $P = .33$), or mean daily pain score at 48 hours post transfusion (51% vs 17% decrease, $P = .35$) in the transfused group.[23] A review of >39 000 admissions in adults with sickle crisis in the US showed that simple transfusion was associated with decreased inpatient mortality and decreased 30-day readmission rate (42.6% to 33.3%), but with increased length of stay. Reasons for admission were multiple and included many for non-pain–related indications.[24] On the basis of current evidence, patients with acute pain should not be transfused unless there is an additional indication for transfusion.[11,12]

Acute chest syndrome

Acute chest syndrome is defined as an acute illness characterized by fever and/or respiratory symptoms in association with a new pulmonary infiltrate on chest radiograph. Severity can vary from a mild self-limiting pneumonic illness to respiratory distress syndrome and multiorgan failure and it can be rapidly progressive.[25] Prospective studies show that between 65% to 72% of patients with ACS are transfused and that both simple transfusion and RCE are associated with improvements in clinical, radiologic, and oxygenation outcomes.[26,27] RCE has been shown to be safe and effective for treating ACS, with 44 children with ACS treated with RCE for worsening respiratory function showing an improvement in clinical outcomes within 24 hours of exchange.[28] Retrospective comparisons of RCE and simple transfusion have been inconclusive, with 1 study in adults showing no significant differences in severity or patients' outcome between RCE and simple transfusion, but a study in children comparing simple transfusion, up-front RCE, or simple transfusion followed by RCE showed that outcomes did not differ between simple transfusion and RCE despite the RCE group having more severe features of ACS.[29] This study supports the recommendations from evidence-based reviews that not all patients with ACS will require transfusion and that the necessity and type of transfusion will depend on clinical severity.[11,25] Simple transfusion to a Hb level of 10 to 11g/dL[26] should be considered in symptomatic ACS with Hb >1.0 g/dL below baseline or if oxygen saturations cannot be maintained >92% on room air or if oxygen requirements increase. RCE should be considered in patients with features of severe disease (eg, worsening hypoxia, increasing respiratory rate, decreasing platelet count, decreasing Hb concentration, multilobar disease on chest radiograph, and neurologic complications) or if patients deteriorate despite initial simple transfusion.[11,25]

In adult patients, an arterial blood gas performed on room air may be useful in guiding treatment decisions and a partial pressure of oxygen <9.0 kPa (65 mm Hg) has been recommended as an indication for transfusion,[25] but transfusion should not be delayed in rapidly deteriorating patients with a lesser degree of hypoxia.[15]

Acute stroke

International guidelines recommend that patients with an acute ischemic stroke should be treated with exchange transfusion aiming for Hb of 10 g/dL and HbS <30%.[11,30] Although there are no RCTs comparing exchange with top-up transfusion, initial treatment with exchange transfusion is associated with a lower risk of subsequent stroke when compared with initial treatment with simple transfusion. If the patient presents with an ischemic stroke and markedly reduced Hb (60 g/dL), an initial simple transfusion may be required, followed by an exchange transfusion to reduce HbS to <30%. Although there is little evidence on the efficacy of transfusion in hemorrhagic stroke,

Table 3. Summary of non-neurological indications for long term transfusion[11,12,15]

Indication	Comment
Recurrent pain crisis	Consider if hydroxyurea ineffective or contraindicated
Recurrent acute chest syndrome	Consider if hydroxyurea ineffective or contraindicated
Recurrent priapism	Consider if lack of response to other treatments
Leg ulcers	Consider if lack of response to other treatments or in context of clinical trial
Pulmonary hypertension	Consider on case by case basis or in context of clinical trial
Post renal or liver transplantation	Consider on case by case basis

exchange transfusion would usually be recommended in this situation in part because of the possibility of neurosurgery.

Acute priapism

Initial management of acute priapism will include pain relief, α-adrenergic agents, and penile aspiration or irrigation. There is no randomized trial evidence of either simple or exchange transfusion in acute priapism, and observational data show variable responses to transfusion. Previous data have described high rates of neurologic complications in patients with priapism receiving exchange transfusions, but these were associated with high posttransfusion Hb levels, which would have been associated with increased viscosity. Patients who do not respond to aspiration and irrigation will need shunt procedures, and these are performed under general anesthesia, so transfusion may be indicated for these patients. Exchange transfusion aiming for Hb of 10 g/dL and HbS <0% could be considered if shunt procedures are not effective in relieving the priapism.

The acutely unwell sickle cell patient

Patients with SCD can present as acutely unwell with multiorgan failure, which may be related directly to their SCD or may be caused by another factor such overwhelming sepsis. Improvement has been seen after exchange transfusion but this has usually been provided in conjunction with organ support in the ICU so it is difficult to elucidate the impact of the RCE alone.[31] In patients with multiorgan failure, exchange transfusion should be performed aiming for S% <30% and Hb of >10 g/dL. Acute intrahepatic cholestasis is another life-threatening complication of SCD characterized by rapid deterioration in liver function tests and hepatomegaly, where observational data suggests that exchange transfusion may be of benefit.

Preoperative blood transfusion

Surgery and general anesthesia are associated with an increased rate of sickle-related complications. A RCT compared a conservative and aggressive preoperative blood transfusion in 604 operations in patients with sickle cell anemia. The conservative regimen (aiming for Hb 10 g/dL) was as effective as the aggressive regimen (aiming for Hb of 10 g/dL and HbS <30%) in preventing perioperative complications, although alloimmunization was more common in the aggressive transfusion group.[32] ACS was the most frequent clinical complications, seen in 10% of patients in both arms of the trial. A subsequent RCT, the TAPS trial (Transfusion Alternatives Pre-Operatively in Sickle Cell Disease) compared preoperative transfusion with no preoperative transfusion in low- and moderate-risk surgical procedures in patients with HbSS or HbSβ^0 thalassemia. Patients randomized to transfusion were given a simple transfusion aiming for Hb of >10 g/dL (if Hb <9 g/dL) or a partial exchange aiming for HbS <60% (if Hb >9 g/dL). Clinically important complications were significantly increased in the nontransfused group (39% vs 15% of patients, $P = .023$) and this difference was primarily explained by a marked increase in ACS in the untransfused group (27% vs 3%).[33]

Patients with HbSS and HbSβ^0 thalassaemia with Hb <9 g/dL undergoing low- and moderate-risk surgery should receive preoperative simple transfusion aiming for a Hb level of 10 g/dL. It is more difficult to recommend optimal preoperative strategy for other groups of patients, including patients with Hb >9 g/dL who only represented 24% of patients in the TAPs trial. The decision for preoperative transfusion where there is no randomized trial evidence should be taken on an individual patient basis, depending on patient phenotype, previous operative history, and type of operation. Patients having high-risk surgery (eg, cardiac or neurologic surgery) should have preoperative exchange transfusion aiming for HbS% of <30%. Similarly, in patients having moderate risk surgery but a very severe phenotype, exchange transfusion may be appropriate. In patients with sickle cell hemoglobin (HbSC), a mild phenotype and Hb> 9 g/dL, it may be appropriate to offer no preoperative transfusion, although scrupulous management of oxygenation and fluid management perioperatively is essential. In patients with HbSC, but a more severe phenotype or previous postoperative complications, pre-operative transfusion should be considered.

There is little evidence about the role of preoperative surgery in the emergency situation, but the risk of performing surgery without blood transfusion needs to be balanced with the risks of delaying surgery. The decision for transfusion will need careful discussion between surgeon, anesthetist, and hematologist. In practice, clinicians should consider a preoperative simple transfusion in patients with Hb <9 g/dL. If the Hb is >9 g/dL, surgery should proceed, with blood being available in case there are postoperative complications. Sometimes (eg, before complex neurological surgery or before renal transplant) it may be advisable to perform emergency exchange transfusion before surgery.

Long-term blood transfusion for disease modification

Long-term transfusion therapy is associated with a large burden to the patient, including the need for regular hospital attendance and often the need to take iron chelation therapy. The decision to embark on a long-term transfusion program should not be undertaken lightly and, particularly where evidence is limited, the patient (and their caregiver/family) should be fully informed of the risks and benefits of transfusion, and their opinion will be paramount in the decision about whether to undergo treatment. This risk-benefit ratio will differ between patients and may also vary in the same patient over time. The rationale for long-term transfusion therapy may change over time and patients on long-term transfusion therapy should be reviewed at least annually to discuss new clinical evidence and their experience of transfusion to enable a decision to be reached in partnership with the patient about whether to continue on the transfusion program. This discussion may be influenced by evidence of efficacy or side effects of transfusion, including iron overload. The non-neurological indications for blood transfusion are summarized in Table 3. The evidence for transfusion for primary or secondary stroke prevention is discussed elsewhere in this issue.

Recurrent pain

Patients randomized to receive transfusion in trials of transfusion vs standard care in primary stroke prevention showed decreased pain episodes when compared with untransfused patients. Analysis of the Stroke Prevention trial data according to treatment received show that hospitalization rates for pain were improved by transfusion (9.7 vs 27.1 events per 100 patient years, $P = .014$)[34] and in the Silent Cerebral Infarct Multi-Centre Clinical Trial, adverse events related to pain were decreased from 102.2 to 41.6 ($P = .04$) in the transfused group.[6] Comparison of rates of recurrent pain in patients randomized between transfusion and hydroxyurea in trials looking at secondary and primary stroke prevention show that transfusion was more effective than hydroxyurea in preventing severe recurrent pain crises. In the Stroke With Transfusions Changing to Hydroxyurea trial, rates of sickle cell anemia pain events were similar in both groups but sickle-related serious adverse events were more common in the nontransfused arm, and most of these were caused by a reduction of

prolonged hospitalization in the transfused patients (7.6% vs 23.9%, $P = .016$).[35] Similarly, in the TCD with Transfusions Changing to Hydroxyurea trial, pain episodes occurred in 2% of transfused patients, compared with 8% of patients on hydroxyurea.[7]

Observational data looking at small numbers of adults with recurrent pain shows that rates of hospital admission because of pain can be reduced by regular automated exchange transfusions. One trial showed a reduction of 70% in emergency admissions and a 40% decrease in days in hospital in 20 patients in the 12 months after commencing regular transfusion,[9] and another showed the median pain crisis rate decreased from 8 crises over 60 months before transfusion to 11 over 415 months once transfusions were commenced.[36]

Transfusion therapy is certainly effective in reducing severe pain episodes and hospitalizations as a result of pain, but hydroxyurea is also effective in reducing the incidence rate of severe pain.[37,38] Hydroxyurea should be used as initial therapy for patients with recurrent pain in view of the decreased costs and side effects associated with its use. Chronic transfusion therapy should be considered in patients with recurrent pain where hydroxyurea has not been effective or is contraindicated.

Prevention of acute chest syndrome

Similarly randomized comparison of transfusion with standard care show a decrease in hospitalization rates for ACS (2.2 vs 15.7 events per 100 patients years, $P = .0001$)[34] and a decrease in ACS adverse events (1.8 vs 14.4 events per patient year, $P < .001$) in the transfused patients.[6] One randomized comparison of hydroxyurea and transfusion showed similar rates of ACS in both groups,[35] and the other showed a decrease in rates of ACS with transfusion (3% vs 7%).[7] A retrospective study of children on chronic transfusion therapy because of recurrent or severe ACS showed a decrease in ACS incidence with transfusion (0.1 vs 1.3 episodes per patient year, $P < .0001$).[39] Hydroxyurea is also effective in reducing rates of ACS[37,38] and should be offered as initial therapy for patients with ACS. As in patients with recurrent pain, chronic transfusion therapy should be considered in patients with ACS where hydroxyurea is not effective or is contraindicated.

Prevention of recurrent priapism

Observational data of the effect of long-term transfusion on the rates of priapism has had mixed results. One paper looking at 10 adults with acute priapism treated with RCE followed by hydroxyurea or chronic transfusion showed that 7 of 10 responded acutely and 2 patients required long-term RCE to prevent recurrence.[40] A further observational trial showed that only 1 of 6 patients with recurrent priapism responded to chronic transfusion.[41] In contrast, the SIT trial prospectively followed up 59 adolescent males who were transfused for 3 years, compared with 52 who were not transfused, and showed a significant decrease in the incidence of priapism (0.8 vs 6.7 adverse events per patient year, $P = .02$).[6] Transfusion can therefore be considered as treatment of patients with recurrent priapism in whom first-line treatments (simple measures and medications) have not worked.

Other indications for long-term transfusion

Transfused patients in the SIT trial also showed significantly decreased rates of symptomatic avascular necrosis of the hip (0.49 vs 2.25 adverse events per patient year, $P = .02$),[6] but there is little evidence to support long-term transfusion in patients with established avascular necrosis. Long-term transfusion has also been suggested to be of benefit in the treatment of leg ulcers, pulmonary hypertension, renal dysfunction, and after renal and liver transplantation.[11,12,15] Transfusion cannot currently be recommended in these situations in the absence of randomized trial data but should be considered in individual cases after consultation with an expert hematologist or as part of a clinical trial.[11,12,15]

Transfusion in pregnancy

Pregnant women with sickle cell disease have an increased rate of maternal and fetal morbidity and mortality. In a recent UK prospective study, 26 of 109 women (24%) were transfused during pregnancy. Transfusion was more common in women with HbSS (45%) than with HbSC (5%). Fifteen of 26 of the transfusions were simple transfusions and 11 of 26 were exchange transfusions; 5 women had a single exchange transfusion and 6 had repeated exchanges through pregnancy.[42] Patients who are pregnant should receive transfusion in the acute situation much as they would do outside pregnancy (ie, if they are acutely anemic or have an acute sickle complication [stroke or ACS]). There is insufficient evidence to suggest a definitive Hb level at which a pregnant woman should be transfused, but transfusion has been suggested if the Hb is <7 g/dL or >2 g/dL below baseline.[15,43]

There is insufficient evidence currently to provide a recommendation on the role of prophylactic transfusion (ie, ongoing transfusion throughout pregnancy) to decrease the associated maternal and fetal complications. Early retrospective observational studies suggested that transfusion may be of benefit but were limited by study size and inconsistent methods of transfusion. One small RCT compared a group of women with sickle cell anemia receiving prophylactic transfusion with a group of women receiving transfusion only on demand. This showed that acute pain episodes were decreased in the transfused group, but it was insufficiently powered to show a significant impact on other maternal or fetal complications.[44] There have been several cohort studies comparing the effects of prophylactic transfusion vs transfusion on demand, and a recent systematic review and meta-analysis reviewed 11 cohort studies and the randomized trial described here.[45] The meta-analysis concluded that prophylactic transfusion was associated with a reduction in maternal mortality, vaso-occlusive pain episodes, pulmonary complications, pulmonary embolism, pyelonephritis, perinatal mortality, neonatal death, and preterm birth. The 2 groups did not differ in odds of pulmonary infection, ACS, urinary tract infection, endometritis, preeclampsia, intrauterine fetal demise, small-for-gestational-age infants or low-birth-weight infants.

It concluded that prophylactic transfusion might benefit pregnant women with SCD but that the studies had a moderate to high risk of bias and were methodologically limited. The studies began transfusion at different gestations and used varying transfusion methodologies and targets, which meant that comparison between them was difficult. For example, even within the RCT the prophylactic transfusions were started either at 8 to 14 weeks gestation in 78% of participants and at 20 to 26 weeks gestation in the remainder. Participants had either simple or partial exchange transfusions to obtain Hb of 10 to 11 g/dL and HbS of $<35\%$.[44,45] Fetal complications in particular may be caused by placental sickling, which occurs very early in pregnancy and therefore if prophylactic transfusion is going to have an impact on fetal well-being (growth and prematurity), it may need to be commenced early in pregnancy. In addition, it is not clear whether anemia or the presence of sickle cells causes vaso-occlusion, which is the primary pathology in pregnancy adverse events, and therefore it is difficult to conclude whether

Table 4. Indications for transfusion in pregnant women with SCD[30,43]

Indication	Comment
Women with previous serious medical, obstetric, or fetal complications	Consider prophylactic RCE
Women who are on transfusion regimen before pregnancy for primary or secondary stroke prevention or for the prevention of severe disease complications	Continue prepregnancy transfusion program
Twin pregnancies	Consider prophylactic RCE as high rate of complications in twin pregnancies
Acute anemia	Simple transfusion if Hb <7 g/dL or >2 g/dL below baseline
Acute chest syndrome, acute stroke, or other acute complication	Emergency RCE followed by prophylactic transfusion thereafter
Repeated pain crises during pregnancy	Emergency RCE followed by prophylactic transfusion thereafter

maintenance of Hb level (by simple transfusion) or reduction of HbS (by RCE) is the optimal transfusion strategy. Although observational studies of prophylactic RCE have shown improvements in fetal birth weights, these were not controlled studies and the role of prophylactic transfusion in pregnancy can only be answered by a RCT.

Current UK guidance recommends that prophylactic transfusion during pregnancy be considered in women with a severe sickle phenotype prepregnancy or in previous pregnancies and in women with twin pregnancies[30,43] (Table 4). If a woman develops sickle complications during pregnancy (eg, ACS, recurrent pain), she should be offered ongoing prophylactic transfusions for the remainder of the pregnancy. Whether this is simple or exchange transfusion will depend on baseline Hb and severity of symptoms. This advice does not differentiate between genotype, and although women with milder sickle genotypes do have less frequent complications during pregnancy, they do have increased adverse events compared with the normal population.[42] In subgroup analysis of the meta-analysis, patients with HbSC receiving prophylactic transfusion had a significant reduction in odds of vaso-occlusive pain and pulmonary embolism only, although these outcomes were based on smaller numbers of patients. A retrospective study of pregnant women with HbSC, published since the meta-analysis compared women receiving prophylactic or on-demand transfusions, showed a significant decrease in sickle-related complications and prematurity in the group receiving prophylactic transfusion.[46] On current evidence, the decision for prophylactic transfusion in pregnancy should be based on a patient-by-patient basis depending on clinical factors.

Conclusions

Blood transfusion remains an important therapeutic intervention for patients with SCD and its use is increasing. Although there are several promising new drugs in early phase trials, none has been licensed to date for use in patients, and despite hemopoietic stem cell transplant and gene therapy now showing that curative interventions are feasible for patients with SCD, the availability of these technologies is still limited.

Transfusions should be offered to patients when the benefits outweigh the risks and inconvenience. Reasons for blood transfusions include a one-off blood transfusion for the treatment of an acute complication and long-term blood transfusion therapy for the prevention or treatment of chronic disease complications, but outside of the prevention of neurologic disease, there is little randomized trial evidence to guide our clinical decision making. The risks and benefits of embarking on a long-term transfusion program, and the method of transfusion, should be fully discussed with the patient and/or family. Evidence about the role of transfusion is regularly being published and advice to patients about transfusion should also be updated regularly. This can be provided as part of a thorough annual review, which should include clinical review, efficacy of transfusion, iron overload, review of indication for transfusion, and discussion of alternatives. There is little evidence comparing hydroxyurea and transfusion, and in view of the evidence showing that use of hydroxyurea in the early years can decrease rates of acute pain and ACS,[37] hydroxyurea should be considered as initial treatment of patients presenting with these complications. There is a need for improved research in this area, particularly for well-designed RCTs to examine the role of transfusion and hydroxyurea in the prevention of the chronic complications of SCD and in the role of prophylactic transfusion during pregnancy.

Acknowledgments

The author thanks Susan Robinson and Rachel Kesse-Adu for reviewing the manuscript.

Correspondence

Jo Howard, Department of Haematology, Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, London SE1 9RT, United Kingdom; e-mail: jo.howard@gstt.nhs.uk.

References

1. Drasar E, Igbineweka N, Vasavda N, et al. Blood transfusion usage among adults with sickle cell disease - a single institution experience over ten years. *Br J Haematol*. 2011;152(6):766-770.
2. Raphael JL, Oyeku SO, Kowalkowski MA, Mueller BU, Ellison AM. Trends in blood transfusion among hospitalized children with sickle cell disease. *Pediatr Blood Cancer*. 2013;60(11):1753-1758.
3. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med*. 1998;339(1):5-11.
4. Adams RJ, Brambilla D; Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) Trial Investigators. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. *N Engl J Med*. 2005;353(26):2769-2778.
5. Ware RE, Helms RW; SWiTCH Investigators. Stroke With Transfusions Changing to Hydroxyurea (SWiTCH). *Blood*. 2012;119(17):3925-3932.
6. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med*. 2014;371(8):699-710.
7. Ware RE, Davis BR, Schultz WH, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. *Lancet*. 2016;387(10019):661-670.
8. Kuo KH, Ward R, Kaya B. Howard J, Telfer P. A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients. *Br Soc Haematol*. 2015;170:425-439.
9. Tsitsikas DA, Sirigireddy B, Nzouakou R, et al. Safety tolerability, and outcomes of regular automated red cell exchange transfusion in the management of sickle cell disease [published online ahead of print 16 February 2016]. *J Clin Apher*. doi:10.1002/jca.21447.

10. Dunbar LN, Coleman Brown L, Rivera DR, Hartzema AG, Lottenberg R. Transfusion practices in the management of sickle cell disease: a survey of Florida hematolgists/oncologists. *ISRN Hematol*. 2012;2012:524513.
11. National Heart, Lung and Blood Institute. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report. 2014. http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines. Accessed 1 October 2016.
12. Davis BA, Allard S, Qureshi A, et al. Guidelines on red cell transfusion in sickle cell disease part 2: indications for transfusion. *Br J Haematol*. In press.
13. Swerdlow PS. Red cell exchange in sickle cell disease. *Hematology Am Soc Hematol Educ Program*. 2006;2006:48-53.
14. Porter JB, Huehns ER. Transfusion and exchange transfusion in sickle cell anaemias, with particular reference to iron metabolism. *Acta Haematol*. 1987;78(2-3):198-205.
15. Howard J, Telfer P. Sickle Cell Disease in Clinical Practice. London: Springer-Verlag; 2015
16. Duclos C, Merlin E, Paillard C, et al. Long-term red blood cell exchange in children with sickle cell disease: manual or automatic? *Transfus Apheresis Sci*. 2013;48(2):219-222.
17. Mian HS, Ward R, Telfer P, Kaya B, Kuo KH. Optimal manual exchange transfusion protocol for sickle cell disease: a retrospective comparison of two comprehensive care centers in the United Kingdom and Canada. *Hemoglobin*. 2015;39(5):310-315.
18. Koehl B, Sommet J, Holvoet L, et al. Comparison of automated erythrocytopheresis versus manual exchange transfusion to treat cerebral macrovasculopathy in sickle cell anemia. *Transfusion*. 2016;56(5):1121-1128.
19. Fasano RM, Leong T, Kaushal M, Sagiv E, Luban NLC, Meier ER. Effectiveness of red blood cell exchange, partial manual exchange and simple transfusion concurrently with iron chelation therapy in reducing iron overload in chronically transfused sickle cell anemia patients. *Transfusion*. 2016 epub
20. Stanley HM, Friedman DF, Webb J, Kwiatkowksi JL. Transfusional iron overload in a cohort of children with sickle cell disease: impact of magnetic resonance imaging, transfusion method and chelation. *Pediatr Blood Cancer*. 2016 epub.
21. Sarode R, Matevosyan K, Rogers ZR, Burner JD, Rutherford C. Advantages of isovolemic hemodilution-red cell exchange therapy to prevent recurrent stroke in sickle cell anemia patients. *J Clin Apher*. 2011;26(4):200-207.
22. Poullin P, Sanderson F, Bernit E, Brun M, Berdah Y, Badens C. Comparative evaluation of the depletion-red cell exchange program with the Spectra Optia and the isovolemic hemodilution-red cell exchange method with the COBE Spectra in sickle cell disease patients. *J Clin Apher*. 2015 epub
23. Kelly S, Deng X, Hoppe C, Styles L. A pilot randomized trial of red blood cell transfusion for acute treatment of vaso-occlusive pain episodes in sickle cell anaemia. *Br J Haematol*. 2015;171(2):288-290.
24. Nouraie M, Gordeuk VR. Blood transfusion and 30-day readmission rate in adult patients hospitalized with sickle cell disease crisis. *Transfusion*. 2015;55(10):2331-2338.
25. Howard J, Hart N, Roberts-Harewood M, Cummins M, Awogbade M, Davis B; BCSH Committee. Guideline on the management of acute chest syndrome in sickle cell disease. *Br J Haematol*. 2015;169(4):492-505.
26. Emre U, Miller ST, Gutierez M, Steiner P, Rao SP, Rao M. Effect of transfusion in acute chest syndrome of sickle cell disease. *J Pediatr*. 1995;127(6):901-904.
27. Vichinsky EP, Neumayr LD, Earles AN, et al; National Acute Chest Syndrome Study Group. Causes and outcomes of the acute chest syndrome in sickle cell disease. *N Engl J Med*. 2000;342(25):1855-1865.
28. Velasquez MP, Mariscalco MM, Goldstein SL, Airewele GE. Erythrocytapheresis in children with sickle cell disease and acute chest syndrome. *Pediatr Blood Cancer*. 2009;53(6):1060-1063.
29. Saylors RL, Watkins B, Saccente S, Tang X. Comparison of automated red cell exchange transfusion and simple transfusion for the treatment of children with sickle cell disease acute chest syndrome. *Pediatr Blood Cancer*. 2013;60(12):1952-1956.
30. Sickle Cell Society. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK. 2008. www.sicklecellsociety.org/wp-content/uploads/2016/02/Standards-for-the-Clinical-Care-of-Adults-with-Sickle-Cell-Disease-in-the-UK.pdf. Accessed 1 October 2016.
31. Hassell KL, Eckman JR, Lane PA. Acute multiorgan failure syndrome: a potentially catastrophic complication of severe sickle cell pain episodes. *Am J Med*. 1994;96(2):155-162.
32. Vichinsky EP, Haberkern CM, Neumayr L, et al; The Preoperative Transfusion in Sickle Cell Disease Study Group. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. *N Engl J Med*. 1995;333(4):206-213.
33. Howard J, Malfroy M, Llewelyn C, et al. The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study: a randomized controlled multicenter clinical trial. *Lancet*. 2013;381:930-938.
34. Miller ST, Wright E, Abboud M, et al; STOP Investigators. Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. *J Pediatr*. 2001;139(6):785-789.
35. Alvarez O, Yovetich NA, Scott JP, et al; Investigators of the Stroke With Transfusions Changing to Hydroxyurea Clinical Trial (SWiTCH). Pain and other non-neurological adverse events in children with sickle cell anemia and previous stroke who received hydroxyurea and phlebotomy or chronic transfusions and chelation: results from the SWiTCH clinical trial. *Am J Hematol*. 2013;88(11):932-938.
36. Kalff A, Dowsing C, Grigg A. The impact of a regular erythrocytapheresis programme on the acute and chronic complications of sickle cell disease in adults. *Br J Haematol*. 2010;149(5):768-774.
37. Wang WC, Ware RE, Miller ST, et al; BABY HUG investigators. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet*. 2011;377(9778):1663-1672.
38. Charache S, Terrin ML, Moore RD, et al; Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med*. 1995;332(20):1317-1322.
39. Hankins J, Jeng M, Harris S, Li CS, Liu T, Wang W. Chronic transfusion therapy for children with sickle cell disease and recurrent acute chest syndrome. *J Pediatr Hematol Oncol*. 2005;27(3):158-161.
40. Ballas SK, Lyon D. Safety and efficacy of blood exchange transfusion for priapism complicating sickle cell disease. *J Clin Apher*. 2016;31(1):5-10.
41. Driss F, Moh-Klaren J, Pela AM, Tertian G. Regular automated erythrocytapheresis in sickle cell patients. *Br J Haematol*. 2011;154(5):656-659.
42. Oteng-Ntim E, Ayensah B, Knight M, Howard J. Pregnancy outcome in patients with sickle cell disease in the UK–a national cohort study comparing sickle cell anaemia (HbSS) with HbSC disease. *Br J Haematol*. 2015;169(1):129-137.
43. RCOG. Management of Sickle Cell Disease in Pregnancy. Green-top Guideline No 61. Royal College of Obstetricians and Gynaecologists, London. Available at https://www.rcog.org.uk/en/guidelines-research-services/guidleines/gtg61/.
44. Koshy M, Burd L, Wallace D, Moawad A, Baron J. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. *N Engl J Med*. 1988;319(22):1447-1452.
45. Malinowski AK, Shehata N, D'Souza R, et al. Prophylactic transfusion for pregnant women with sickle cell disease: a systematic review and meta-analysis. *Blood*. 2015;126(21):2424-2435, quiz 2437.
46. Benites BD, Benevides TC, Valente IS, Marques JF Jr, Gilli SC, Saad ST. The effects of exchange transfusion for prevention of complications during pregnancy of sickle hemoglobin C disease patients. *Transfusion*. 2016;56(1):119-124.