Transfusion in the Patient With Sickle Cell Disease: A Critical Review of the Literature and Transfusion Guidelines

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The clinical outcomes of sickle cell disease (SCD) have vastly improved over the years in great part as a result of advanced medical technologies, improved patient education, and multidisciplinary care. A key component in the successful management of patients with SCD is red blood cell transfusion therapy used in the treatment and prevention of sickle cell complications. However, although the successful application of transfusion therapy has significantly improved the morbidity and mortality of patients with SCD, the literature that addresses the appropriate selection and use of blood products continues to evolve with no clear universal standard of care. Our objectives were to provide an in-depth review of the current literature on transfusion therapy in SCD and to provide a set of guidelines for the transfusion management of patients with SCD.

ADVANCES IN THE treatment and risk stratification of sickle cell disease (SCD) within the past few decades have led to marked improvements in morbidity and survival. Whereas 30 years ago the average life span of a patient with SCD was 14 years, more recent estimates show an average life span of 42 years for men and that of 48 years for women.1 Today, optimal management begins with early intervention involving newborn screening and prophylactic penicillin. Further management includes multidisciplinary care in a comprehensive center where patients receive ongoing support in the form of education, multiorgan screening, and advanced clinical therapies targeting the prevention and treatment of complications associated with SCD. One of the key components in the management of patients with SCD is transfusion, usually packed red blood cell (RBC), therapy. The major goals of RBC transfusion in the setting of SCD include the following: (1) improving the oxygen-carrying capacity by increasing the total hemoglobin (Hgb) level; (2) decreasing blood viscosity and increasing oxygen saturation by diluting the concentration of sickle Hgb (Hgb S); and (3) suppressing endogenous production of sickle RBCs by increasing tissue oxygenation.2-4 Overall, RBC transfusion in the patient with SCD helps improve symptomatic anemia as well as prevent and resolve vaso-occlusive events that result in acute chest syndrome (ACS), stroke, and other ischemic organ damages. Although the implementation of RBC transfusion has served to reduce complications and improve quality of life among patients with SCD, it is not without adverse effects. Thus, both appropriate and judicious use of transfusion therapy are important.

TRANSFUSION THERAPY

Red blood cell transfusion therapy in SCD can be divided into 2 major categories, intermittent and chronic. Intermittent transfusions are generally administered in the acute setting at different times to treat various manifestations of SCD, whereas chronic transfusions are performed primarily on a scheduled basis to prevent complications or their progression. The transfusions may be further classified as prophylactic or as therapeutic. Simple and exchange (automated and manual) RBC transfusions are the 2 methods available to accomplish intermittent and chronic transfusion management in SCD. Simple transfusions are those administered with a single dose of RBCs. Conversely, exchange transfusions entail a much higher volume of RBCs being administered (ie, total blood volume = 1-2) with simultaneous removal of the patient’s RBCs. The amount of RBCs exchanged is determined by the goal with which to lower the patient’s Hgb S level (ie, <30%). Table 1 highlights the transfusion
types, methods, and indications for adults and children with SCD. Although some of the indications for transfusion therapy have been studied and validated in randomized prospective trials, many have been based on anecdotal and/or observational studies.

Although it is clear from these studies that transfusion therapy is effective in the management of SCD, there is currently no detailed set of guidelines recommending a uniform standard of care. As a result, transfusion practices in SCD remain disparate throughout nationwide academic centers. A recent letter to the editor by Afenyi-Annan and Brecher helped illustrate this point. Their letter reported on a survey of 50 academic medical centers regarding the use of phenotype-matched RBCs for transfusion in patients with SCD. The results showed that 27 of the 37 academic centers that responded to the questionnaire provided RBC minor antigen matching to prevent alloantibody development and that different antigens were selected for matching among these centers that did phenotypically match. The authors concluded that, despite the common approach by some of the academic centers, there is currently no single standard of care with regard to RBC product selection for the prevention of RBC alloimmunization.

More recently, a College of American Pathology study that examined 1182 laboratories in North America to determine the extent of RBC minor antigen phenotype testing of nonalloimmunized patients with SCD as well as the use of phenotypically matched RBC units in the transfusion of patients with SCD was conducted. The results of the survey indicated that approximately 63% of the laboratories surveyed did not routinely phenotype patients with SCD past ABO and D. Of 37% of the laboratories that did perform additional antigen phenotyping beyond ABO and D, 75% gave phenotypically matched RBC units to patients with SCD. The conclusions from the College of American Pathology survey were as follows: (1) most North American hospitals do not determine the RBC antigen phenotype of nonalloimmunized patients with SCD past ABO and D and (2) the laboratories that do determine the red cell antigen phenotype of nonalloimmunized patients with SCD past ABO and D most commonly match for C, E, and K antigens when phenotypically similar red cell units are to be transfused. The results from both cited national surveys underscore the lack

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of and therefore the potential need for unified practice in the use of RBC product selection for transfusion therapy in patients with SCD in an effort to prevent alloimmunization.

INDICATIONS AND GUIDELINES FOR INTERMITTENT TRANSFUSIONS

This section outlines the indications for intermittent transfusions and provides evidence-based information that assisted our formulation of recommendations for RBC transfusion therapy. The rationale and method of transfusion are addressed under specific indications. Most of the indications classified under this heading are for the treatment of acute manifestations of SCD requiring therapeutic transfusions. However, there are a couple of indications that are prophylactic, in which patients are transfused before specific surgical procedures.

**Acute Symptomatic Anemia**

Individuals with SCD are chronically anemic and will often remain asymptomatic despite their low Hgb levels. In general, anemic patients with SCD who are clinically stable and have a high reticulocyte count should not be treated with transfusion therapy. However, when acute symptomatic anemia develops, often in the setting of blood loss, increased RBC destruction, suppression of erythropoiesis, or sequestration of RBCs, therapeutic intermittent transfusion of RBCs is warranted. This type and method of transfusion is a first-line therapy and serves to ameliorate the symptoms of cardiac and respiratory compromise associated with acute symptomatic anemia and is recommended as the therapy in this situation. The decision to give additional RBC products beyond the first dose should be individualized for each patient and depends mostly on whether symptoms of acute anemia persist. There is no recommendation regarding a specific target Hgb/hematocrit level; however, in general, patients with SCD should not be overtransfused at an Hgb level higher than 10 g/dL.

**Aplastic Crisis**

Aplastic crisis is defined as a decrease in the Hgb level of more than 3 g/dL with reticulocytopenia. In patients with SCD, a common cause of aplastic anemia is infection of hematopoietic precursors by Parvovirus B19. Because marked suppression of erythropoiesis occurs for up to 7 to 10 days, coupled with an RBC life span of only 12 to 15 days, patients with SCD often have a precipitous decrease in RBCs after marrow infection with Parvovirus B19. After several days, the body compensates for the inadequate production of RBCs by expanding plasma volume, which, if left untreated, can lead to a high output or congestive heart failure. As with acute symptomatic anemia, therapeutic intermittent RBC transfusion is a first-line therapy and is recommended to correct low Hgb levels and prevent cardiac decompensation. Specifically, administration of the RBC unit in adults should be given slowly (1 mL/kg per hour) to avoid fluid overload. In children, a dose of 10 mL/kg can be given in 2 aliquots, with each aliquot transfused over a 4-hour period. Occasionally, diuretic therapy between aliquots is required to avert or decrease the risk for pulmonary edema. The alternative transfusion method of partial manual exchange transfusion (removal of whole blood and replacement with packed RBCs) may also be an effective way to increase the Hgb concentration, but without adding excess volume. This transfusion strategy can be considered as a second-line therapy and should be considered in patients who have an increased susceptibility to fluid overload owing to cardiac or renal dysfunction.

**Acute Splenic or Hepatic Sequestration**

Splenic or hepatic sequestration occurs when sickled RBCs become trapped within the sinusoids, leading to organ engorgement and a reduction in intravascular RBCs. When a significant proportion of the circulating RBC population becomes entrapped, symptomatic anemia ensues. The fatality rate of splenic sequestration approaches 10%, and episodes can be recurrent.

First-line therapy. Intermittent simple transfusion is the recommended treatment for acute splenic sequestration. Hemoglobin measurements after transfusion are often higher than what would be expected from standard RBC transfusion dosing, suggesting that the spleen unloads RBCs upon transfusion, an event otherwise known as autotransfusion. Therefore, when transfusing packed RBCs in this context, half of the standard dose (in children, 3-5 mL/kg) may be initially administered to observe the extent of autotransfusion that occurs. In this situation, one would not
want to inadvertently overtransfuse and cause hyperviscosity, which can occur when Hgb reaches levels higher than 10 to 12 g/dL. Overall, the effects of a therapeutic simple transfusion are rapid resolution of anemia and reduction of spleen size.

**Second-line therapy.** In some infants who develop recurrent events of splenic sequestration, short-term prophylactic chronic simple transfusion protocols (with a similar percentage of Hgb S goals as that for stroke therapy, <30%) can be initiated and continued until they are 2 years old, by which time their spleen can be removed. However, high rates of recurrence have been shown to still occur with limited chronic transfusion protocols administered every 3 to 4 weeks. Chronic transfusions are therefore not recommended as a first-line intervention to prevent the recurrence of splenic sequestration, but they can be considered in young high-risk infants and younger children who are ineligible for splenectomy.

**Acute Stroke**

In the natural history of SCD, several cohort studies have estimated that the chance of developing a clinical stroke by the age of 18 to 20 years is 11%. This estimate however does not reflect the implementation of transcranial Doppler (TCD) screening tests that resulted from a stroke prevention trial in sickle cell anemia (Stroke Prevention [STOP] trial). In the STOP trial, stroke rates were compared between 63 children who received intermittent simple transfusions and 67 children who received standard supportive care. All the children were at high risk for a first-time stroke because of their elevated cerebral blood flow as measured on TCD screening tests. The results of the STOP trial demonstrated a 90% relative decline in stroke rates in the transfusion group as compared with the standard care group, leading to the implementation of prophylactic chronic simple RBC transfusion protocols administered monthly in children at high risk for stroke. Furthermore, the STOP trial also confirmed the use of TCD screening as an effective means to identify children with SCD who are at high risk for a first-time stroke. Current guidelines suggest screening with TCD every 6 months in patients with SCD between 2 and 16 years old. Normal screen results are defined as a velocity lower than 200 cm/s. Patients with SCD with TCD readings higher than 200 cm/s on 2 occasions are candidates for prophylactic RBC transfusions, the details of which are discussed in Indications and Recommendations for Chronic Transfusions on chronic transfusion indications. In a retrospective study on first stroke rates among California children with SCD between 1991 and 2000, Fullerton et al observed a decrease in stroke rates after the implementation of the STOP trial. As a result, the incidence of primary stroke in children with SCD is declining.

**Pediatric recommendations.** For children who do develop an acute stroke, treatment with RBC exchange should be performed as soon as possible to rapidly reduce Hgb S levels and curtail the progression of the neurovascular sickling event. Anecdotal evidence had suggested that transfusion in the acute setting should aim for an Hgb concentration between 9 and 10 g/dL and an Hgb S concentration lower than 30%. Dramatic recovery of neurologic function after RBC exchange transfusion has been documented. As the management of patients with SCD continues to extend survival, more adult patients with SCD and stroke will be seen. Data from the Cooperative Study of SCD reported a higher occurrence of infarctive strokes in children and a higher occurrence of hemorrhagic strokes in adults. Because most data on the prevention and treatment of stroke are in children, the question of how to treat adult patients with SCD who have experienced a stroke remains: are they managed like children with SCD or similar to how adults without SCD are? Without enough data at this time to support either management option, current recommendations are to follow the guidelines for adult patients without SCD, with only a few modifications pertinent to patients with SCD. In all cases, stroke type identification is helpful in determining the management course of action. Ischemic stroke is treated with either antiplatelet agents or a tissue plasminogen activator. The risk for brain hemorrhage after tissue plasminogen activator treatment is approximately 6% and should be treated with intermittent simple transfusion of packed RBCs, fresh frozen plasma, and platelets, whereas, in acute hemorrhagic strokes, the treatment approach is the same for patients with SCD and those without SCD; the only difference is consideration of a preangiogram transfusion in the former group.
**Acute Chest Syndrome**

Acute chest syndrome (ACS) is defined as a new pulmonary infiltrate on chest x-ray accompanied by respiratory symptoms, chest pain, or fever. According to the Cooperative Study of SCD, approximately 30% of patients with SCD will develop ACS at least once in their lifetime and half will develop one or more recurrent episodes. In a Dallas newborn cohort study, ACS was reported to be one of the most common causes of death, second only to infection. Red blood cell transfusion early in the course of ACS is recognized as an important component in treatment. Intermittent simple and acute exchange transfusions contribute to immediate therapeutic options depending on the clinical situation. Immediate exchange transfusion has been shown to rapidly improve ACS if instituted within 48 hours after diagnosis. Therapeutic simple transfusion has similarly been shown to improve symptoms if implemented within 24 hours of diagnosis. Miller and Rao from the State University of New York Downstate Medical Center recently published a letter to the editor describing their success with simple transfusions in the management of early ACS. They emphasized caution that the practice of executing exchange transfusions before simple transfusions may cause delays in treatment that lead to irreversible progression of ACS—damage that could potentially be avoided with early simple transfusions. However, in comparable observational studies, others have demonstrated that patients continued to develop worsening symptoms associated with ACS despite having undergone simple transfusions. Currently, the recommendation is to give a simple transfusion in patients with less serious respiratory compromise. For patients with a progressive decline in PaO\(_2\) (<60 mm Hg in adults and <70 mm Hg in children) or rapid clinical deterioration, therapeutic exchange transfusion is recommended.

**Acute Multiorgan System Failure**

Acute multiorgan system failure is a severe and life-threatening complication of SCD and often entails involvement of the lungs, liver, or kidneys. Although its etiology is not precisely known, it is believed to be the end result of multiple infarctive episodes secondary to vascular occlusion from sickled RBCs. Multiorgan system failure may occur after multiple episodes of severe pain crisis in patients with SCD. Therapeutic intermittent simple and exchange transfusions are recommended during acute organ failure and have been shown to rapidly reverse organ dysfunction and improve clinical symptoms. In a retrospective study performed by Hassell et al, of 1067 patients with SCD reviewed, 14 were found to have acute multiorgan failure, defined as the development of severe dysfunction of at least 2 of 3 major organs during a pain episode. Among those 14 patients, 17 episodes of acute multiorgan failure were identified. In all cases, aggressive transfusion therapy, equivalent to a mean of 8 U of RBCs transfused in a simple transfusion and a mean of 9 U of RBCs transfused in an exchange transfusion, was associated with increased survival and rapid recovery of organ function in all but 1 episode. Although small studies support the use of RBC transfusion in the setting of acute multiorgan failure, the onset, duration, and type of RBC transfusion (simple vs exchange) in these settings are unclear. General consensus and anecdotal experience suggest that the recommendations at this time be that therapeutic simple transfusion is indicated if severe anemia is present. However, in patients with higher Hgb levels or relatively more severe organ failure, therapeutic exchange transfusion may be a more suitable choice because it avoids the possibility of overtransfusion while rapidly reducing the percentage of Hgb S.

**Severe Infection**

Complications from infection are some of the leading causes of morbidity and mortality in patients with SCD. Patients with SCD are at an increased risk for infection because they become functionally asplenic over time. Severe infection alone is not an indication for intermittent transfusion. However, therapeutic intermittent simple transfusions should be considered in patients with SCD and a concomitant infection who develop symptomatic anemia.

**Before Surgery Requiring General Anesthesia**

General anesthesia is known to place patients with SCD at higher risk of developing intravascular sickling, which results in higher rates of morbidity and mortality during the perioperative period. Prospective studies comparing patients with SCD who received a simple transfusion with individuals who did not receive transfusion clearly showed that transfusion therapy decreases the rate of postoper-
In 1995, Vichinsky et al. set out to compare conservative transfusion regimens with aggressive transfusion regimens in the perioperative management of SCD. The aggressively treated group was designed to maintain a preoperative Hgb level of 10 g/dL and an Hgb S level of 30% or lower. This was accomplished with either prophylactic exchange transfusions or repeated simple transfusions. The conservatively treated group maintained a preoperative Hgb level of 10 g/dL without regard for the Hgb S level. This was achieved by prophylactic simple transfusions only and with less overall units transfused as compared with the aggressively treated arm of the study. As a result, the mean Hgb S level in the conservatively treated group was 59% and that in the aggressively treated group was 31%. The results of the study showed comparable rates in perioperative complications between the 2 groups but significantly fewer complications in the conservative group. The authors concluded that conservative transfusion was just as effective as aggressive transfusion in preventing perioperative complications and was associated with half as many transfusion-related complications. However, there is still controversy over the optimal preoperative transfusion regimen. Griffin and Buchanan described a retrospective analysis of 54 patients undergoing 66 elective surgical procedures without preoperative transfusion and 10 children undergoing 10 elective procedures with preoperative transfusion. They concluded that a less aggressive transfusion regimen (no preoperative transfusion) was needed for children with SCD and for those patients who were clinically stable with regard to cardiorespiratory status and near their anemia baseline level undergoing elective minor surgical procedures (eg, hemorrhhaphy, dental/oral surgery, ophthalmologic surgery, and tympanostomy tube placement) under general anesthesia.

Before Eye Surgery

Eye surgery is typically performed under local anesthesia; however, the microvascular nature of the surgery coupled with the importance of preventing permanent eye damage warrants the use of perioperative transfusion therapy. Early studies promoted the use of prophylactic exchange transfusion in eye surgery, but more recent studies do not seem to support such an approach. The management of patients with SCD undergoing an eye surgery should follow the same guidelines for patients with SCD undergoing surgery requiring general anesthesia as described in the previous section.

INDICATIONS AND RECOMMENDATIONS FOR CHRONIC TRANSFUSIONS

Prevention of Recurrent Stroke in Children

Approximately 3.75% of patients with SCD will experience during their lifetime one or more cerebrovascular accidents. It is estimated that without therapeutic intervention, up to 70% of those who experienced a first stroke will develop a recurrent stroke within 2 to 3 years. Chronic RBC transfusion is critical in reducing the risk for a recurrent stroke. With long-term transfusion therapy, the risk for a recurrent stroke is reduced by up to 90%. The recommended guideline for prophylactic chronic transfusion is to give a simple transfusion every 3 to 4 weeks while maintaining an Hgb S level lower than 30% and a hematocrit level of 30% or lower. Alternatively, prophylactic chronic RBC exchange transfusion can be performed in lieu of chronic simple transfusion while maintaining the same target hematocrit and Hgb S levels. Several observational studies looked into the ideal Hgb S level to maintain to prevent a recurrent stroke. Cohen et al. demonstrated in a small study on 15 patients that maintenance of the Hgb S level at 50% rather than at 30% after 3 years of neurologic...
stability showed no increased risk for a recurrent stroke. Furthermore, by reducing the transfusion burden, a significant decrease in cost and transfusion-related complications was noted. Conversely, a study by Peglow et al\textsuperscript{26} showed that 7 of 16 transient ischemic events and 5 of 6 recurrent infarctions occurred in patients with SCD with an Hgb S level higher than 30%. Overall, the guideline of maintaining Hgb S levels at 30% is what is most frequently quoted in the literature and most often practiced. Some institutions will however accept an Hgb S level of up to 50\% after 3 years of neurologic stability. The duration of chronic transfusion after an initial stroke remains unclear.

A few studies have indicated that patients with chronic transfusions that were stopped when they were 18 years old showed no recurrence of stroke in subsequent years, whereas other studies have demonstrated a high rate of recurrent ischemic events within 12 months of transfusion cessation.\textsuperscript{28,29} Recently, the STOP II trial was initiated to study whether children with SCD at high risk for stroke could safely stop receiving scheduled chronic transfusions after a minimum of 30 months. The trial was stopped early because of the finding that there was a return to a high risk for stroke among children who stopped receiving chronic RBC transfusion protocols. Although the STOP II trial was designed to examine the duration of transfusions for the prevention of an initial stroke, continuing RBC transfusions to prevent a recurrent stroke can be extrapolated from the STOP II trial. The result is that most sickle cell centers now recommend continuation of prophylactic chronic transfusion regimens indefinitely to prevent recurrent strokes.

Prevention of a First Stroke in Children

The STOP trial in 1998 by Adams et al\textsuperscript{10} set a new precedent in identifying and prophylactically treating children with SCD at high risk for a first stroke. In children with SCD, the most frequent cause of brain infarction is blockage of the internal carotid and middle cerebral arteries. With blockage, high blood-flow velocity is seen and can be detected by TCD. Screening children with SCD by TCD can therefore identify children at high risk for a first stroke. In the STOP trial cohort, children identified with abnormal blood-flow velocities were randomly assigned to either standard care or prophylactic chronic transfusion. The patients in the transfusion arm of the study were transfused with either simple or exchange transfusion. The goal was to adjust the Hgb S to a level lower than 30\% within a period of 21 days without exceeding an Hgb concentration of 12 g/dL or a hematocrit level of 36\%. Once the Hgb S reached a level lower than 30\%, the children would then receive transfusions every 3 to 4 weeks. The results of the study showed that 11 strokes occurred in the standard care group vs only 1 stroke in the transfusion group. The difference in stroke reduction (91\%; \( P < .001 \)) in the transfusion group was significant enough that it led to early termination of the study. At the present time, most sickle cell centers regularly screen children with TCD and will begin prophylactic chronic transfusions (by the simple or the exchange method) every 3 to 4 weeks in those individuals with repeatedly high blood-flow rates.\textsuperscript{9,26}

In 2000, the STOP II trial was initiated to determine whether children with SCD at high risk for stroke could stop receiving blood transfusions after a minimum of 30 months. This multicenter randomized clinical trial had recruited up to 79 patients when it was stopped 2 years earlier in November 2004. At the time the trial was stopped, of the 41 patients who had been randomly assigned to stop receiving transfusions, 14 reverted back to a high risk for stroke as measured by TCD and 2 had suffered a stroke. In comparison, none of the patients who were assigned to continue receiving blood transfusions developed stroke or reverted to a high stroke risk. In light of the STOP II trial results, children with SCD at high risk for a first-time stroke who begin chronic blood transfusions are recommended to continue receiving chronic transfusion protocols indefinitely to prevent an initial stroke.

Complicated Pregnancy

Prophylactic transfusion is not an indication in patients with SCD undergoing a normal pregnancy.\textsuperscript{30} However, complications associated with pregnancy are often indications for therapeutic simple or exchange transfusion. Preeclampsia/eclampsia, twin pregnancy, previous perinatal mortality, acute renal failure, sepsis, bacteremia, severe anemia, ACS, hypoxemia, anticipated surgery with general anesthesia, and infusion of angiographic dye are conditions that may require limited prophylactic chronic transfusion therapy. In
all cases, the degree of anemia determines the best method of transfusion. When the Hgb concentration is lower than 5 g/dL and the reticulocyte count is lower than 3%, a simple transfusion administered slowly is recommended. If the Hgb level is between 8 and 10 g/dL or higher, an exchange transfusion is recommended with a target post-transfusion Hgb level of 10 g/dL and a post-transfusion Hgb S level of 50% or lower.31

Chronic Renal Failure

Patients with renal failure develop progressive anemia as a result of loss of erythropoietin production by the kidney. In these patients, prophylactic chronic transfusion in the form of simple transfusion helps avoid severe symptomatic anemia.

CONTROVERSIAL INDICATIONS FOR ACUTE OR CHRONIC TRANSFUSIONS

Frequent Pain Episodes

Patients who suffer from frequent severe pain episodes may benefit from chronic transfusion therapy. Similar to the protocol for stroke prevention, simple or exchange transfusion every 3 to 4 weeks with a target Hgb S level lower than 30% may lead to symptomatic improvement.

Recurrent Acute Chest Syndrome

Multiple episodes of ACS have been implicated in the development of restrictive lung disease, leading to severe pulmonary fibrosis, pulmonary hypertension, and cor pulmonale. There are some observational data to suggest a beneficial role for transfusion therapy in patients with severe pulmonary hypertension from hemolysis.32 However, it is not known whether pulmonary hypertension secondary to restrictive lung disease would benefit from transfusion therapy as it possibly does in hemolysis-associated pulmonary hypertension. Although there is no information to support the use of transfusion therapy in recurrent ACS, some authors have advocated the use of chronic transfusion protocols as a means to prevent end-stage lung disease.33 In a recent article by Hankins et al,34 27 children with SCD received chronic simple transfusion therapy for the prevention of new episodes of ACS and recurrent or unusually severe ACS was retrospectively evaluated. They found that the incidence of ACS decreased from 1.3 to 0.1 episodes per patient-year (P < .0001). However, the median severity score for ACS episodes was not statistically significantly altered. The investigators concluded that chronic transfusion therapy reduces the incidence of events but does not lessen their severity. They advocated prospectively comparing the effectiveness of chronic transfusion therapy with that of hydroxyurea and stem cell transplantation. Unfortunately, further evidence is needed to support the efficacy of such programs.

Prevention of Pulmonary Hypertension/Cor Pulmonale

Pulmonary hypertension and its related complications are increasingly being recognized as some of the most common causes of mortality in patients with SCD. Retrospective studies demonstrated that hemolysis-associated pulmonary hypertension is seen in 20% to as much as 60% of patients with SCD.35,36 Studies comparing SCD-associated pulmonary hypertension and primary pulmonary hypertension showed lower pulmonary pressures and higher cardiac output in the former group yet similar mortality rates in both groups. The implication that relatively lower pulmonary pressures in patients with SCD run a comparable risk for sudden death as in patients with primary pulmonary hypertension underscores the importance of identifying and possibly treating patients with SCD with even mild elevations in pulmonary pressure. Recently, Gladwin et al36 designed a prospective study on the prevalence and prognostic significance of pulmonary hypertension in the SCD population. Doppler echocardiography was performed on 195 patients looking into tricuspid regurgitant jet velocity. Pulmonary hypertension was defined as a regurgitant velocity of at least 2.5 m/s. The results of the study identified Doppler-defined pulmonary hypertension in 32% of the patients. In addition, a tricuspid regurgitant velocity of at least 2.5 m/s conferred an increased risk for death as compared with velocities lower than 2.5 m/s (rate ratio = 10.1; P < .001). In 9% (n = 17) of the patients, severe pulmonary hypertension, defined as a tricuspid regurgitant jet velocity higher than 3 m/s, was identified. For these patients, exchange transfusion, oxygen, and other vasodilator therapies were offered. Of the 17 patients with severe pulmonary hypertension, 11 began either an aggressive exchange transfusion program or an inhaled nitrous oxide therapy after diagnosis; of these 11 patients, 10 were still alive at the time this article was written.
The study by Gladwin et al. introduced the use of Doppler echocardiography to identify patients with SCD at the early and possibly reversible stages of pulmonary hypertension. Similar to the application of TCD in the detection of patients with SCD at high risk for a first stroke, Doppler echocardiography may enable clinicians to aggressively treat and prevent end-stage pulmonary hypertension in patients with mild elevations in pulmonary pressure. Anecdotal evidence and early studies suggest that transfusion therapy may be beneficial in not only reducing the progression of pulmonary hypertension but also possibly reversing an early disease. Although the potential use of transfusion therapy is promising in this area, additional data are needed before transfusion therapy can be recommended for patients with a tricuspid regurgitant velocity higher than 2.5 m/s.

Priapism

The current first-line treatment for acute priapism entails adequate hydration and pain control. Alternatively, case studies have suggested improvement in patients after exchange or simple transfusion. Despite this, no randomized control trial has been performed to compare transfusion therapy with hydration and adequate pain control. In addition, there is an association among SCD, priapism, exchange transfusion, and subsequent neurologic events that has been described in patients, and this has been termed the ASPEN syndrome. As a result, most centers opt to manage priapism without transfusion until it becomes persistent for longer than 24 to 48 hours, during which transfusion becomes the second-line therapy. The indications and preferred methods of transfusion therapy in the management of priapism require additional studies before further transfusion guidelines can be recommended.

Acute Pain Crisis

Acute pain crisis is the most common cause of hospital admission among patients with SCD. Management of acute pain crisis has been well documented. The mainstay of treatment is adequate pain management with hydration. Studies by Platt et al. showed less frequent episodes of pain crisis with higher degrees of anemia. Transfusion therapy could therefore worsen symptoms of acute pain crisis and is not recommended in the treatment of acute pain crisis.

Normal Pregnancy

Currently, uncomplicated pregnancies in patients with SCD are not an indication for transfusion therapy. The guidelines for such care stem from a prospective study by Koshy that compared prophylactic transfusions with no transfusion in pregnant women with SCD. The results of that study showed no significant difference in perinatal outcomes or in medical or obstetric complications between the 2 study groups. In the end, Koshy concluded that prophylactic transfusions should be omitted from the management of pregnant women with SCD without harm to the mother or the fetus.

Leg Ulcers

Previous studies have demonstrated no difference in the rate of healing in leg ulcers when treated with transfusion vs no transfusion. As a result, most experts agree that there is no role for transfusion therapy in the management of leg ulcers in patients with SCD.

METHODS OF TRANSFUSION THERAPY

Several methods of transfusion are available to patients with SCD, and determining the optimal method often depends on the clinical situation and the resources available. When deciding on which method to use, it is important to consider the unique conditions associated with SCD and thus select a method of transfusion that does not exacerbate the underlying pathophysiology of the disease. For instance, patients with SCD often have expanded plasma volumes in response to chronic anemia. When expanded plasma volumes are combined with cardiac dysfunction in some patients with SCD, the increase in blood volume from acute transfusion can often precipitate volume overload and congestive heart failure. In these cases, the use of diuretic therapy or splitting of RBC units can be considered. Alternatively, exchange transfusions can often be used as a means of increasing Hgb levels without significantly increasing the total blood volume.

Another important consideration in SCD is related to changes in blood viscosity from the transfusion of RBCs. Sickled blood in any state has an increased viscosity as compared with normal Hgb. In normal arterial blood, the optimal hematocrit level is approximately 40%. In sickled blood, the optimal hematocrit level is dependent on
oxygen tension, ranging from 18% at a PaO₂ level of 18 mm Hg to 31% for fully oxygenated blood. Depending on the concentration of Hgb S, transfusion of normal RBCs can either greatly increase or have a minimal impact on viscosity. In general, performing simple transfusion when the Hgb S concentration is higher than 60% will profoundly increase viscosity, but simple transfusion when the

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<th>Approximate volume (mL)</th>
<th>Composition</th>
<th>Hematocrit level (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs</td>
<td>250</td>
<td>200 mL of red cells; 50 mL of plasma; 100 mL of adenine saline solution</td>
<td>&lt;50-80</td>
<td>Made from WB; Storage at 4°C; Contains 10^8 WBCs; Cannot be infused as rapidly as WB because of increased viscosity.</td>
</tr>
<tr>
<td>RBCs (additive solution)</td>
<td>350</td>
<td>200 mL of red cells; 50 mL of plasma; 100 mL of adenine saline solution</td>
<td>50-60</td>
<td>Made from WB; Storage at 4°C; Contains 10^8 WBCs; Red cell product most commonly available.</td>
</tr>
<tr>
<td>Prestorage leukocyte-reduced RBCs</td>
<td>250-350</td>
<td>Depends on additive solution and anticoagulant</td>
<td>50-80</td>
<td>Made from WB; &lt;5 x 10^6 WBCs; ≥85% of original red cell mass; Does not prevent TA-GVHD.</td>
</tr>
<tr>
<td>Washed RBCs</td>
<td>200</td>
<td>180 mL of RBCs; 20 mL of isotonic saline (0.9%)</td>
<td>–</td>
<td>Washing removes most of the plasma and approximately 80% of leukocytes.</td>
</tr>
<tr>
<td>Irradiated RBCs</td>
<td>250-350</td>
<td>Depends on additive solution and anticoagulant</td>
<td>–</td>
<td>Reduces storage time because of potassium leak after irradiation; Prevents TA-GVHD; Storage 28 d after irradiation or by original expiration date, whichever comes first.</td>
</tr>
<tr>
<td>Frozen deglycerolized RBCs</td>
<td>200</td>
<td>180 mL of RBCs; 20 mL of isotonic saline/dextrose solution</td>
<td>–</td>
<td>Usually reserved for rare blood phenotypes; May be stored frozen for 10 y; Plasma reduced.</td>
</tr>
</tbody>
</table>

Abbreviations: WB, white blood; WBC, white blood cell; TA-GVHD, transfusion-associated graft-vs-host disease.


*Citrate, phosphate buffer, adenine, and dextrose.

|Addendum: adenine, dextrose, saline, and mannitol (most plasma removed and replaced with additive solution).
Hgb S concentration is lower than 40% will cause minimal changes in viscosity. These observations provide the rationale for targeting a posttransfusion hematocrit level of approximately 30% to reduce viscosity and the risk for vaso-occlusion. Furthermore, therapeutic acute exchange transfusions can be considered over simple transfusions in cases in which there is a need to not only bring the Hgb and hematocrit up to an optimal level but also reduce the Hgb S level rapidly.

Acute simple transfusions involve infusion of normal donor RBCs into the patient without removal of the patient’s own RBCs. As previously mentioned, acute simple transfusions are most effective in situations requiring an immediate increase in oxygen-carrying capacity without the need to reduce the level of Hgb S. Again, it is important to avoid transfusing at a posttransfusion hematocrit level higher than 30% because higher hematocrit levels are associated with poorer oxygen delivery.

Chronic simple transfusions provide several benefits to patients with SCD; they increase the oxygen-carrying capacity of blood, dilute the concentration of Hgb S, and chronically suppress production of sickled RBCs. In the average-sized adult, transfusion of 2 to 3 U of RBCs every 3 to 5 weeks is typically sufficient to keep the Hgb S concentration lower than 30%. If necessary, the total volume of transfused RBCs can be adjusted according to the pretransfusion level of Hgb A. Ideally, Hgb A levels should be higher than 70%; any level lower may require larger transfusion volumes or more frequent transfusions.

Exchange transfusions can be performed either manually or through an automated apheresis instrument, a process termed erythrocytapheresis. The advantages of exchange transfusions over simple transfusions are their ability to rapidly adjust the hematocrit level and Hgb S concentration with less risk for iron and fluid overload. In most centers, erythrocytapheresis is used to perform RBC exchange more commonly than the manual method. There are however instances when manual exchange is indicated. For instance, an emergency situation in which access to an automated instrument is unavailable or delayed is one potential indication for rapid partial manual exchange. Another is the size of the patient. Of note is that when performing manual exchange, there are 3 requirements needed to ensure a safe and effective manual exchange: (1) increases in blood viscosity should be avoided; (2) blood volume should be maintained throughout the exchange; and (3) the exchange should be completed as quickly as possible. As in all cases, the factors cited need to be considered for every unique clinical situation and adjusted accordingly.

Selection of Anticoagulant-Preservative Solutions

All RBC units collected are placed in one of several anticoagulant-preservative solutions. Examples of some solutions include CPDA-1, CPD, and ACD-A. In all of these solutions, the basic components are composed of citrate, dextrose, and/or adenine. Additive systems (ASs) are also available (AS 1, AS 3, and AS 5) and can be added to RBC units at the time of collection as a means to extend the shelf life of the blood product (Table 2). These solutions contain additional adenine and/or mannitol to help further preserve RBC units. In adults, there is no contraindication or limitation to using any of the anticoagulant-preservative solutions in the acute or chronic transfusion setting. In children, there are some concerns regarding the effects of additional adenine and mannitol found in AS RBCs. Both substances in large amounts have been implicated in renal toxicity and adverse shifts in body fluids in neonates and small infants. However, studies have shown that small-volume transfusions (<20 mL/kg) of RBCs stored in ASs and given to neonates do not lead to an increased risk for adverse outcomes. In the setting of chronic or large-volume transfusions, there is not enough information to support in one way or another the use of AS RBC transfusions in small children. As a result, practical guidelines suggest avoiding the use of AS RBCs in these settings or in patients with comorbidities such as renal or hepatic dysfunction.

ADVERSE EFFECTS OF TRANSFUSION THERAPY INCLUDING PREVENTION AND MANAGEMENT

Despite the beneficial effects of transfusion therapy in SCD, there are still adverse effects associated with transfusion that can lead to serious short- and long-term complications. The following sections discuss the adverse effects from transfusion and strategies for their prevention.

Immune-Related Adverse Effects

Febrile nonhemolytic transfusion reactions. A common adverse effect of transfusion therapy is the
development of febrile nonhemolytic transfusion reactions (FNHTRs). The incidence of FNHTRs occurs in 0.5% to 1% of transfusions. In such reactions, white blood cells stored in the blood product release cytokines that cause fever and chills. Although these reactions are self-limited and benign, they are problematic in patients with SCD because they often mimic the symptoms seen in more serious complications of SCD, such as infection and pain crisis. A widely established and accepted method in reducing the incidence of FNHTRs is the administration of blood products that are leukocyte reduced. For reasons beyond the prevention of FNHTRs, it is recommended that all patients with SCD receive leukocyte-reduced cellular blood products.

### Table 3. Average Frequencies of RBC Alloantibodies Made By Transfused Patients With SCD

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Average frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-E</td>
<td>21</td>
</tr>
<tr>
<td>Anti-K</td>
<td>18</td>
</tr>
<tr>
<td>Anti-C</td>
<td>14</td>
</tr>
<tr>
<td>Anti-Le^a</td>
<td>8</td>
</tr>
<tr>
<td>Anti-Fy^a</td>
<td>7</td>
</tr>
<tr>
<td>Anti-Jk^b</td>
<td>7</td>
</tr>
<tr>
<td>Anti-D</td>
<td>7</td>
</tr>
<tr>
<td>Anti-Le^b</td>
<td>7</td>
</tr>
<tr>
<td>Anti-S</td>
<td>6</td>
</tr>
<tr>
<td>Anti-Fy^b</td>
<td>5</td>
</tr>
<tr>
<td>Anti-M</td>
<td>4</td>
</tr>
<tr>
<td>Anti-E</td>
<td>2</td>
</tr>
<tr>
<td>Anti-C</td>
<td>2</td>
</tr>
</tbody>
</table>


In the days before the implementation of extended phenotype matching in patients with SCD, studies reported an estimated alloimmunization rate ranging from 19% to 43% in transfused patients with SCD. Interestingly, multiply transfused patients without SCD had an alloimmunization rate of approximately 5%, indicating that patients with SCD were at a significantly higher risk of developing alloimmunization to RBC antigens. In a comprehensive study on the frequency of and risk factors associated with alloimmunization in patients with SCD, Vichinsky et al suggested that the increased alloimmunization rate in patients with SCD was likely caused by antigenic differences between patients with SCD (most of whom were of African descent) and most blood donors (most of whom were white).

The realization that antigenic differences in the random donor units were the primary cause for the disproportionately high alloimmunization rates in patients with SCD has resulted in several studies in the past 10 years looking into cost-effective and practical ways to locate more compatible units for the SCD population. One retrospective study performed by Sosler et al proposed a model to reduce alloimmunization in patients with SCD by selecting units from a donor blood pool consisting of random black donors only. The rationale behind this model was based on data that the chance of finding a unit with the phenotypes E, C, Fya, K, and Jkb was 93% in the black population and was 7% in the white population. However, no prospective trial has been performed to show that such an approach would reduce the rate of alloimmunization. Furthermore, many experts are wary about the social implications of racially labeling blood. Expanding on the idea of using a select pool of donors has led to the implementation of limited donor pool programs in which a select group of donors is repeatedly tapped to provide blood that is antigenically matched with that of patients with SCD.

Ambruso et al reported that such a limited donor program can reduce by 10-fold the incidence of alloimmunization in transfused patients with SCD. However, their study was plagued with administrative problems, including difficulties in recruiting donors of African descent, inventory management, distribution and transfusion of the matched blood, and the increased expense of the program. For the past several years, the American
Red Cross in Atlanta, Georgia, has been using a program entitled Partners for Life (PFL) in which patients with SCD receive transfusions from a pool of 9 to 10 dedicated donors with similarly antigen-matched units. If units from the patient’s donor pool were unavailable, the patient would then receive similarly antigen-matched units from random donors. Recently, a retrospective review by Hillyer et al showed that, although the PFL program was successful in accomplishing an alloimmunization rate of 7%, it was not successful in limiting the exposure of patients with SCD to a small dedicated blood donor pool. The result of this review led to the revision of the PFL program to an antigen matching program only.

Despite the difficulties in establishing a limited donor program, the strategy to antigen match donor RBCs with recipient RBCs has been proven to be effective in reducing the rate of alloimmunization. Past data have shown that the most commonly made alloantibodies that form in SCD are directed against C, E, and K antigens (Table 3). In a prospective study by Vichinsky et al, partial RBC phenotype matching in a stroke prevention trial in SCD demonstrated a decrease in the alloimmunization rate (from 3% to 0.5% per unit) and a subsequent reduction in hemolytic transfusion reactions by 90%. The authors thus recommended that all transfused patients with SCD be antigen matched for E, C, and K antigens. Another study by Tahhan et al looked into more extensive phenotype matching in RBC transfusions. From their data, they showed that none of 40 transfused patients with SCD who were matched for C, E, K, Fya, Fyb, and S antigens developed alloantibodies as compared with 16 of 46 patients who did develop alloantibodies after receiving matched and unmatched transfusions.

Although the data suggest that the more antigens phenotypically matched between donors and recipients there are, the less likely alloantibodies will develop, most experts agree that it is impractical to perform complete phenotype matches between donors and recipients with SCD. In a retrospective study by Castro et al, of 351 transfused patients with SCD reviewed, 29% developed alloantibodies while receiving cross-matched compatible blood. From this group, they calculated that 53.3% of the 137 alloimmunizations observed would have been prevented if transfusions had been selected by limited phenotypes (C, c, E, e, and K). They further calculated that 70.8% of the alloimmunizations observed would have been prevented if the antigens S, Fya, and Jkb were added to the original phenotype match (extended phenotype-matching protocol). On the other hand, the authors pointed out that approximately 13.6% of the random donor population would be expected to match the limited phenotype-matching protocol but that only 0.6% would match the extended phenotype-matching protocol. As a result, the authors concluded that trying to match with an extended phenotype is impractical as a long-term strategy. Overall, the following recommended strategy recognizes the importance of limited phenotype matching and strikes a balance between reducing alloimmunization rates and maintaining a sufficient pool of acceptable donors. For patients without prior alloantibody formation, antigen matching should be performed for C, E, and K antigens. For those patients with previously made alloantibodies, antigen matching should be performed on C, E, K, Fya, Jkb, and other alloantibodies already formed. Most importantly, special efforts should be made to encourage blood donation from people of African descent to add greater diversity to the donor pool and increase the chances of finding compatible units.

**Autoimmunization to RBC antigens.** The presence of autoantibodies to RBC antigens has been observed in the transfusion of patients with SCD. Castellino et al reported the frequency of autoantibody formation as approximately 7.6% in a large review of multiply transfused children with SCD. They also reported a strong association between autoantibody formation and the presence of alloantibodies. The etiology behind the formation of these autoantibodies is poorly understood. As a result, not much information exists to suggest ways in which to lower the incidence of autoantibody formation. Clinically, it is important to recognize that posttransfusion hemolysis in which both autologous and transfused RBCs are destroyed may occur in patients with SCD. The recommended treatment in clinically significant cases is the administration of corticosteroids with or without intravenous immunoglobulin.

**alloimmunization to Human leukocyte antigen or platelet-specific antibodies.** In recent years, the option of bone marrow or stem cell trans-
plantation has been used as a possible curative treatment for patients with SCD. Because of this, special consideration needs to be given to prevent alloimmunization to human leukocyte antigen (HLA). In a report by Friedman et al, 85% of patients with SCD receiving 50 or more transfusions developed alloimmunization to HLA or platelet-specific antibodies. Because platelet refractoriness is a serious complication during bone marrow or stem cell transplantation, it is prudent to prevent alloimmunization as early as necessary in the management of patients with SCD. Current guidelines recommend leukoreduction of RBCs for all patients with SCD receiving transfusion.

Nonimmune-Related Adverse Effects

Iron overload. Simple chronic transfusions over time will lead to iron overload. Patients who develop iron overload may be treated with long-term chelation therapy in the form of deferoxamine. Although deferoxamine is an effective means to reduce iron accumulation, it is an expensive treatment and often difficult to administer, thereby resulting in poor compliance by patients. However, compliance with chelation therapy may improve with the use of oral iron chelation (ie, deferasirox). An alternative to chelation therapy is the use of chronic erythrocytapheresis in lieu of simple transfusions as a way of preventing iron overload. The data involving chronic erythrocytapheresis suggest that iron accumulation can be significantly reduced in chronically transfused patients with SCD. In those patients in whom iron accumulation has already taken place, chronic erythrocytapheresis may reduce ferritin levels, but it does not negate the need for chelation therapy. Overall, chronic erythrocytapheresis appears to be most beneficial when started early in the course of transfusion therapy, before significant iron accumulation occurs.

The use of chronic erythrocytapheresis has demonstrated multiple benefits over chronic simple transfusions, such as more effective management of SCD complications and the reduction of iron accumulation. However, the disadvantages of chronic erythrocytapheresis include increased blood product exposure and increased costs over simple chronic transfusions. Observational studies on the risk for alloimmunization caused by more units used with chronic erythrocytapheresis over chronic simple transfusions demonstrated the following results: in 43 patients studied, only 1 patient developed an alloantibody during erythrocytapheresis treatment. As for cost, Hilliard et al calculated an increased cost for erythrocytapheresis ($36,085 per year) as compared with simple chronic transfusions ($26,058 per year). However, when the added cost of chelation therapy is factored in, the overall costs support the use of chronic erythrocytapheresis not only as a safer and more effective means of chronic transfusion but also as a more economical option in the long-term therapy for patients with SCD.

Transfusion-transmitted infections. With the advent of improved donor screening procedures, the risk for transmission of infectious agents has been substantially reduced since the early 1990s. In general, patients with SCD should feel confident that the risk of contracting an infection from transfusion is very low. The risk of developing transfusion-transmitted diseases in the United States is quite low (1:2 to 4 million for HIV per RBC unit transfused). Thus, it is a generally accepted practice that blood products should not be withheld if an appropriate indication for transfusion is established. Adverse events related to transfusion should always be considered with the clinical need for transfusion on an individual patient basis.

CONCLUSIONS

Red blood cell transfusion is an integral component in the prevention and treatment of complications associated with SCD. In the acute setting, there is an extensive literature to support the use of therapeutic intermittent simple RBC transfusions for the treatment of symptomatic anemia, multiorgan system failure, splenic sequestration, stroke, and ACS. For the prevention of SCD complications, episodic transfusions can be considered in patients requiring general anesthesia before surgery or undergoing microvascular eye surgery. Large multicenter randomized studies such as the STOP I and STOP II trials currently advocate the indefinite use of prophylactic (manual or exchange) chronic RBC transfusions in patients at high risk for stroke as determined by TCD screening.

Although the use of RBC transfusions in the management of SCD has greatly reduced the morbidity and mortality of SCD, their judicious use is warranted given the potential for adverse effects. Immune-related adverse effects, including
FNHTRs and alloimmunization to HLAs, can best be prevented by providing leukocyte-reduced blood products. Optimization for the prevention of RBC antigen alloimmunization can best be handled by implementing national guidelines to provide phenotypically matched RBC units for C, E, and K antigens. Nonimmune-related adverse effects associated with chronic simple transfusions, such as iron overload, are best treated using iron chelation therapy. However, potential prevention of iron overload may be accomplished using erythrocytapheresis as an alternative or complementary therapy.

The treatment guidelines outlined in this article attempt to provide the most recent evidence-based medicine approaches regarding transfusion in the setting of SCD. More research is needed for certain complications for which the use of transfusion has not been clearly defined. In the areas in which transfusion therapy has been studied, it is evident from the literature that use of RBC transfusion has improved the morbidity and mortality of patients with SCD. Further research in these areas will continue to refine and improve these guidelines and ultimately improve the efficacy and safety of blood transfusion therapy in patients with SCD.

REFERENCES