# Management of Patients with Sickle Cell Disease Using Transfusion Therapy

## Guidelines and Complications

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**KEYWORDS**

• Sickle cell disease • Red blood cell transfusion • Alloimmunization • Iron overload

**KEY POINTS**

- Urgent or emergent red blood cell transfusion is indicated for acute ischemic stroke, acute chest syndrome, splenic or hepatic sequestration, transient aplastic crisis, multisystem organ failure, intrahepatic cholestasis, or obstetric complications in patients with sickle cell disease (SCD).
- Chronic transfusion therapy is indicated for primary and secondary stroke prevention and short-term for prevention of splenic sequestration recurrence.
- Patients with SCD should receive red cells antigen matched for C, E, and K to reduce alloimmunization risk.
- The iron status of chronically transfused patients with SCD should be closely monitored and iron chelation therapy and/or erythrocytapheresis implemented to maintain iron balance.

### INTRODUCTION

Over the past few decades, significant advances in the care of patients with sickle cell disease (SCD) have led to improvements in morbidity and survival. The average life span of patients with SCD has increased from 14 years in 1973 to more than 50 years.[1] A key component in the management of patients with SCD is red blood cell (RBC)

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transfusion therapy. The major goals of RBC transfusions are relief of anemia, reduction of circulating sickle hemoglobin (HbS) erythrocytes, and improvement in oxygen-carrying capacity.[2] Although transfusion can be lifesaving, it is not without adverse effects. Using evidence-based transfusion policies can minimize transfusion-related complications. This review addresses RBC transfusion methods, indications (**Table 1**), and complications.

## METHODS OF TRANSFUSION THERAPY

RBC transfusions can be administered by simple or exchange transfusion. Exchange transfusion is preferably performed by automated erythrocytapheresis but can be performed manually. Simple transfusions are dosed in units (1–3 units for adults) or

**Table 1**
**Indications for transfusion therapy in adults and children with sickle cell disease**

| Transfusion Indication | Transfusion Method |
|---|---|
| Generally accepted indications for transfusion | |
| Acute ischemic stroke | Exchange transfusion preferred |
| Primary stroke prevention | Chronic simple or exchange transfusion[a] |
| Secondary stroke prevention | Chronic simple or exchange transfusion[a] |
| Acute chest syndrome (acute) | Simple or exchange transfusion[a] |
| Acute splenic sequestration | Simple transfusion |
| Acute splenic sequestration, recurrence | Chronic simple transfusion (before splenectomy)[b] |
| Preoperative (when general anesthesia required) | Simple transfusion |
| Transient aplastic crisis | Simple transfusion |
| Acute multisystem organ failure | Simple or exchange transfusion[c] |
| Acute hepatic sequestration | Simple or exchange transfusion[c] |
| Acute intrahepatic cholestasis | Simple or exchange transfusion[c] |
| Acute sickle or obstetric complications during pregnancy | Simple or exchange transfusion[c] |
| Controversial indications for transfusion | |
| Acute chest syndrome (recurrent) | Chronic simple or exchange transfusion[c] |
| Vasoocclusive painful episode (recurrent) | Chronic simple or exchange transfusion[c] |
| Pulmonary hypertension | Chronic simple or exchange transfusion[c] |
| Transfusion generally not indicated | |
| Uncomplicated vasoocclusive painful episode | NA |
| Priapism | NA |
| Uncomplicated pregnancy | NA |
| Leg ulcers | NA |
| Nonsurgically managed avascular necrosis | NA |

*Abbreviation:* NA, not applicable.

[a] Exchange transfusion may be preferred in rapidly deteriorating patients when emergent HbS reduction is needed or when there are concerns for post-transfusion hyperviscosity due to a high pretransfusion hemoglobin (ie, >9 g/dL).

[b] Chronic transfusion may be used to delay but not prevent the need for splenectomy in very young children (ie, <2 years) who are at increased risk for invasive pneumococcal infections.

[c] Exchange transfusion may be preferred in patients with iron overload.

volume (10–20 mL/kg for children). Exchange transfusion requires a higher volume of RBCs administered (1.0–1.5 × patients' RBC volume) but simultaneously removes patients' RBCs. Erythrocytapheresis offers the advantage of rapidly reducing HbS independent of the hematocrit and minimizes iron accumulation. Exchange transfusion is often preferred for emergent HbS reduction in patients with higher pretransfusion hemoglobin (Hb)(>9 g/dL) because of hyperviscosity concerns and to prevent iron overload. The decision to use simple versus exchange transfusion depends on specific clinical needs and availability of resources, including apheresis equipment and technical support, adequate supply of antigen-negative donor units, and the potential need for central venous access.[3–5] Partial manual exchange (PME) is an alternative method for patients with a higher Hb (>8.5 g/dL) and involves phlebotomy of 5 to 10 mL/kg (depending on patients' baseline Hb and tolerance) immediately before transfusion. PME has been used to slow progression of transfusional iron overload when used as a chronic transfusion regimen.[6]

## INDICATIONS

### *Acute Splenic Sequestration*

RBC transfusion is indicated for acute exacerbation of anemia occurring with splenic sequestration. Because splenic involution is usually complete by 5 years of age in hemoglobin SS and Sβ° thalassemia, acute splenic sequestration most commonly affects young children. The spleen becomes acutely engorged with sequestered blood and may result in a precipitous decrease in Hb level. Severe episodes may lead to hypovolemic shock and death from cardiovascular collapse within hours. Immediate RBC transfusion will correct the anemia and hypovolemia, but patients should be transfused cautiously to prevent hyperviscosity after splenic sequestration resolves. Aliquots of 5 mL/kg may be administered along with close monitoring of the spleen size, Hb level, and cardiovascular status. In cases of severe sequestration and anemia with hypovolemic shock, initial transfusion with 10 mL/kg packed RBCs (PRBCs) is appropriate. Relapse of acute splenic sequestration is frequent, with 50% to 75% of patients experiencing recurrent episodes.[7] Chronic RBC transfusion to prevent recurrence has not been prospectively studied but is often used to delay definitive treatment of splenectomy in very young children. In a retrospective multicenter study of 190 children with hemoglobin-SS or Sβ° disease, 29% were managed with a blood transfusion program and, overall, 37% ultimately required splenectomy.[7] However, 54% of patients were managed with close monitoring and without prophylactic blood transfusion or splenectomy, of which 59% did not experience a recurrent episode.

### *Transient Aplastic Crisis*

Human parvovirus B19 infects erythrocyte precursors and temporarily suppresses erythropoiesis that can result in severe anemia given the shortened life span of RBCs in patients with SCD. In a single-institution observational study of parvovirus B19–induced red cell aplasia, the median nadir Hb was 4.8 g/dL and 49 of 68 pediatric patients (72%) received a transfusion.[8] The need for transfusion depends on the severity of the anemia, whether they are in the reticulocytopenia stage, and the clinical status of patients. Because anemia associated with red cell aplasia is subacute, patients are typically euvolemic and physiologically compensated. RBC transfusion should be administered slowly with serial small aliquots to prevent congestive heart failure. Parvovirus aplastic crisis typically does not recur because of long-term humoral immunity.

### *Acute Chest Syndrome*

Acute chest syndrome (ACS) describes a new pulmonary infiltrate and respiratory findings, including cough, dyspnea, or new-onset hypoxia, in patients with SCD and is often accompanied by fever. Triggers include infection, pulmonary fat embolism, hypoventilation/atelectasis, and bronchospasm. ACS is the leading cause of death and second most common cause of hospitalization among patients with SCD. The management is primarily supportive and includes respiratory therapy, antibiotics, and, often, RBC transfusion. There have been no randomized controlled trials comparing either simple or exchange transfusion versus no transfusion for ACS. However, in a large epidemiologic study of ACS, transfusion was associated with a shorter duration of hospitalization, suggesting an association with clinical improvement.[9] A difference in efficacy of simple transfusion compared with exchange transfusion as measured by length of hospital stay was not detected in a small study of 20 patients with ACS.[10] In practice, simple transfusion should be considered for any patient with ACS and hypoxemia or acute exacerbation of anemia. Exchange transfusion is typically reserved for patients who are not sufficiently anemic to accommodate a simple transfusion or those with progressive respiratory decline or persistent hypoxia despite oxygen supplementation or simple transfusion.

No prospective randomized trial has been performed to determine the efficacy of chronic transfusion therapy to prevent recurrent ACS. Chronic transfusion therapy is sometimes offered, particularly to individuals who experienced a severe or life-threatening episode. A dramatic reduction in hospitalization for ACS was observed in children undergoing chronic transfusion for primary stroke prevention compared with the observed group, suggesting chronic transfusions may prevent recurrent episodes.[11] In one single-institution study, chronic transfusion therapy reduced the incidence of ACS events among patients with recurrent ACS but did not significantly impact episode severity.[12] Although hydroxyurea is indicated for the prevention of recurrent ACS,[13] future studies are needed to compare chronic transfusion therapy and hydroxyurea for recurrent ACS prevention.

### *Acute Sickle Hepatopathy*

Acute hepatic sequestration and sickle cell intrahepatic cholestasis (SCIC) are severe forms of hepatic injury from vascular occlusion of liver sinusoids.[14] Acute hepatic sequestration manifests as painful enlarging hepatomegaly with a concurrent decrease in hematocrit, reticulocytosis, direct hyperbilirubinemia, and mild transaminitis. Although acute hepatic sequestration rarely results in end organ failure, simple or exchange transfusion is often necessary to resolve the hepatopathy and anemia.[15] However, overly aggressive simple transfusion should be avoided to prevent acute hyperviscosity syndrome resulting from rapid release of intrahepatic RBCs back into the circulation with resolved sequestration.

SCIC is the most severe form of acute sickle hepatopathy, with an overall mortality rate of 40% to 50% in adults and 30% in children due to uncontrolled bleeding and fulminant liver failure.[14] SCIC manifests with sudden onset of right upper quadrant abdominal pain, significantly elevated transaminases (>1000 mg/dL), severe hyperbilirubinemia (total serum bilirubin often >50 mg/dL), coagulopathy, hepatomegaly, renal insufficiency, and acute liver failure in severe cases.[16] Patients can have recurrent episodes, and a subset develop chronic progressive disease that evolves into progressive liver failure.[17] Limited reports describe outcomes based on transfusion management. Ahn and colleagues[18] reviewed 22 cases (7 pediatric, 15 adults) of

severe sickle hepatopathy in the literature that met criteria for SCIC; 7 of 9 patients who received exchange transfusion survived compared with 1 of 13 patients who did not receive erythrocytapheresis. Although this data set is limited, it supports a role for exchange transfusion in the management of SCIC, particularly acute SCIC.[15,17] Correction of coagulopathies with plasma, cryoprecipitate, and platelet transfusions is also often necessary. Maintaining HbS levels less than 30% by chronic erythrocytapheresis has been proposed for patients with recurrent episodes of acute SCIC or chronic progressive hepatopathy.[17]

### *Multisystem Organ Failure*

Multisystem organ failure (MSOF) is a life-threatening complication of SCD resulting from diffuse microvascular occlusion, which usually develops several days after a severe vasoocclusive crisis (VOC). MSOF is characterized by rapid lung, liver, and/or kidney dysfunction and is typically accompanied by a precipitous decrease in the Hb level and platelet count, fever, encephalopathy, and rhabdomyolysis. In addition to broad-spectrum antibiotics, mechanical ventilation, pharmacologic and/or mechanical hemodynamic support, and renal replacement therapy, the use of RBC transfusion can be life saving. The largest retrospective report of SCD-associated MSOF included 17 episodes occurring after unusually severe VOCs.[19] All patients except one recovered with aggressive transfusion support via either multiple simple transfusions or an exchange transfusion. The National Heart, Lung, and Blood Institute (NHLBI)–appointed SCD expert panel recommends immediate simple or exchange transfusion for MSOF because of the gravity of this severe sickle-related manifestation.[15]

### *Preoperative Transfusion Management*

Perioperative conditions, including suboptimal hydration, poor oxygenation, and acidemia, can lead to SCD-related complications, such as ACS, painful VOC, and infections. The Transfusion Alternatives Preoperatively in SCD (TAPS) trial demonstrated that preoperative transfusion is associated with decreased perioperative complications.[20] The TAPS trial compared outcomes of preoperative transfusion versus no transfusion in patients with HbSS or undergoing low-risk or medium-risk surgery. The study was terminated early because of an imbalance of adverse events occurring in the no-preoperative-transfusion arm, with 13 of 33 (39%) individuals experiencing a clinically important complication compared with 5 of 34 (15%) patients who were transfused preoperatively. Ten of 11 serious adverse events were ACS: 9 in the no transfusion and one in the transfusion group. The trial did not include individuals with hemoglobin SC or $S\beta^+$ thalassemia, and poor enrollment of patients requiring low-risk procedures hampered the determination of optimal management for this surgical category.[20] A prior randomized control trial showed that preoperative simple transfusion to achieve a Hb of 10 g/dL is equally effective in preventing postoperative complications compared with erythrocytapheresis to decrease the HbS level to less than 30%.[21] Taken together, patients with SCD should receive a simple transfusion preoperatively to increase the Hb to 10 g/dL for medium- to high-risk surgery.

### *Neurologic Complications*

In children with SCD, the routine use of transcranial Doppler (TCD) screening coupled with chronic transfusion therapy has decreased the prevalence of overt stroke from 11% to 1%.[22] However, neurologic complications in children and adults with SCD remain a major cause of long-term morbidity. Acute ischemic stroke is managed

with RBC transfusion to reduce the HbS level to less than 30% to prevent progression of cerebral ischemia. Exchange transfusion at the time of stroke presentation may be associated with a lower risk of subsequent stroke compared with simple transfusion,[23] but no prospective study has directly addressed this question. In practice, erythrocytapheresis is the preferred transfusion method for initial treatment of an acute stroke. A simple transfusion may be considered for immediate treatment because it may require several hours to establish central venous access, crossmatch multiple PRBC units, and mobilize the apheresis team for erythrocytapheresis.

An evidence-based approach to the management of acute hemorrhagic stroke in patients with SCD is lacking.[22,24] In the largest case series, 15 adults with SCD with subarachnoid hemorrhage from ruptured intracranial aneurysms were treated with partial exchange transfusion in the acute setting before cerebral angiography.[25] Given the lack of formal studies to guide management of hemorrhagic strokes in individuals with SCD, transfusion in the acute setting to decrease the HbS to less than 30% is recommended in addition to therapy for acute intracranial hemorrhage for the general population, including blood pressure management and seizure control.[22,24]

Stroke recurs in 60% to 90% of patients without therapeutic intervention[26] and decreases to approximately 20% with chronic RBC transfusions when the HbS is maintained at less than 30%.[27,28] Although a controlled clinical trial is lacking, standard care for secondary stroke prevention is chronic transfusion therapy. Indefinite therapy is recommended, as discontinuation after short-term or long-term prophylactic transfusions has led to recurrent stroke, even with transition to hydroxyurea.[29] The randomized phase 3 trial, Stroke With Transfusions Changing to Hydroxyurea, addressed transition to hydroxyurea for patients with a history of stroke and iron overload. The trial was closed because of statistical futility on the composite end point of iron overload resolution and stroke prevention. At the time of study closure, no strokes occurred in patients receiving transfusions with chelation, but 7 patients (10%) receiving hydroxyurea and phlebotomy had a new stroke. Moreover, patients receiving chronic transfusion for secondary stroke prevention are still at risk for silent cerebral infarcts (SCIs),[27,30] and cerebral vasculopathy progression.[27,31,32] Taken together, transfusion remains the optimal choice for managing individuals with SCD and stroke.

Children with SCD at the highest risk of overt stroke can be identified by abnormally high blood flow velocities on TCD ultrasound. The Stroke Prevention Trial for sickle cell anemia study (STOP) demonstrated that chronic transfusion therapy decreased the rate of initial stroke in children with an abnormal TCD by 92% compared with the observation arm.[33] Transfusion reduces cerebral blood-flow velocities, in part because of correction of the anemia, which contributes to lower stroke risk. Universal adoption of routine TCD screening and primary prophylactic transfusion therapy for at-risk patients has resulted in significantly decreased rates of first stroke.[34–36] The STOP2 trial supported the use of chronic transfusion indefinitely, as discontinuation after 30 months resulted in an increased rate of abnormal TCD conversion and overt stroke as well as a higher occurrence of SCIs.[37,38]

Based on previous studies demonstrating that hydroxyurea can lower TCD velocities in patients with SCD,[39,40] the Transfusions Changing to Hydroxyurea (TWiTCH) trial (ClinicalTrials.gov: NCT01425307) aimed to compare the efficacy of hydroxyurea with transfusion therapy for children with abnormal TCDs but no primary stroke. The TWiTCH study ended in 2014 at the first interim analysis after data indicated the trial had reached its primary end point; preliminary results showed that hydroxyurea is not inferior to chronic RBC transfusion in lowering TCD velocities in children with abnormal

TCDs. Given the burden of chronic transfusion therapy and because most children with abnormal TCDs will not have a stroke if untreated, the ability to prevent stroke with hydroxyurea is a significant advance.

SCI is more common than overt stroke and is associated with increased risk of overt stroke, new or enlarged SCIs, poor academic achievement, and lower IQ.[41–43] The Silent Infarct Transfusion trial demonstrated that chronic transfusion therapy significantly reduced the incidence of recurrent cerebral infarcts in patients with SCIs at baseline, no history of overt stroke, and normal TCD velocities.[44] Notably, 6 of 99 children (6%) assigned to transfusions had an event (1 stroke, 5 new or enlarged SCIs) compared with 14 of 97 children (14%) in the observation group (7 strokes, 7 new of enlarged SCIs). Because approximately 25% of children with SCD have SCIs,[42,45] the resources needed to provide chronic transfusions to this group would be immense. Whether hydroxyurea can prevent new SCIs or overt stroke in patients with SCIs is not known. Future studies are also needed to determine whether patients with magnetic resonance angiography–defined vasculopathy but normal TCD velocities would benefit from RBC transfusions to prevent vasculopathy progression and/or silent or overt strokes.

## CONTROVERSIAL INDICATIONS

### *Pulmonary Hypertension*

Pulmonary arterial hypertension (PAH) is a common complication in adults with SCD and imposes an increased risk of death. The incidence of PAH diagnosed by right heart catheterization (RHC) is between 6% and 11% in adults with SCD.[46–48] Mortality in these patients is approximately 35% to 40% at 3 to 6 years from diagnosis.[47,48] RHC is the gold standard for diagnosing PAH; but noninvasive evaluations, including tricuspid regurgitant jet velocity (TRV) by Doppler echocardiography, serum N-terminal pro–brain natriuretic peptide (NT-pro-BNP), and the 6-minute walk distance, can be used to predict the presence of PAH and estimate mortality risk.

There are no randomized control trials of hydroxyurea or transfusion therapy for patients with SCD and PAH. The American Thoracic Society (ATS) recommends hydroxyurea for all patients with HbSS who have a TRV of 3.0 m/s or greater alone or TRV of greater than 2.5 m/s with either an elevated NT-pro-BNP level or RHC-confirmed PAH based on studies showing the benefits of hydroxyurea in reducing morbidity and mortality in SCD.[49,50] Transfusion may prevent chronic regional pulmonary hypoxia by reducing the frequency of ACS and decreasing nitric oxide depletion, which results from chronic hemolysis, both of which are risk factors for PAH in SCD.[51] Because transfusion may reverse or stabilize PAH in its early stages by mitigating these pulmonary endothelial effects, the ATS recommends that chronic transfusion therapy be offered to patients who are not responsive to or not candidates for hydroxyurea.[51,52] A recent cross-sectional study of children and young adults with HbSS or HbS$\beta^{\circ}$ supports this recommendation by demonstrating a protective effect of chronic transfusions on pulmonary vascular disease defined by lower TRV measurements.[53] Further investigation is needed to determine if either chronic transfusions or hydroxyurea impact mortality.

### *Pregnancy in Sickle Cell Disease*

Pregnant women with SCD have a higher risk of obstetric complications, including preeclampsia/eclampsia, venous thromboembolism, intrauterine fetal demise, preterm birth, intrauterine growth restriction, and SCD-related complications, including

prepartum and postpartum VOC and ACS. Greater than 50% of patients with SCD have a pain crisis during pregnancy,[54] and 28% will have VOC at the time of delivery.[55] Additionally, approximately 20% of women develop ACS during pregnancy.[56] Furthermore, the maternal mortality rate is 16 times higher and fetal death at delivery is twice as likely in pregnant women with SCD.[57]

Because hydroxyurea may be teratogenic, RBC transfusion is the only disease-modifying therapy for pregnant women with SCD. Transfusion is indicated for women with acute medical or obstetric complications, but conflicting data exist regarding the benefit of regular prophylactic transfusion during pregnancy. Prophylactic transfusion has been proposed to prevent SCD-related and obstetric complications toward the end of pregnancy when they are most frequent. Transfusion may be initiated at 28 weeks' gestation with the goal of maintaining an HbS less than 35% and an Hb of 10 to 11 g/dL.[58] This prophylactic transfusion strategy significantly reduced pain crises and symptomatic anemia but had no effect on pregnancy outcomes in 2 small trials involving 98 women with SCD conducted in the 1980s.[59,60] Recently, prophylactic erythrocytapheresis initiated either in the second or third trimester has been shown in a small single-center retrospective cross-sectional study to be safe and effective in prevention of SCD-related events.[61] Future studies are required to determine if prophylactic transfusions during pregnancy can decrease maternal and perinatal morbidity and mortality associated with SCD. Currently, most obstetricians provide selective transfusion to address specific complications that arise during pregnancy for women with SCD.

### *Leg Ulcers*

Leg ulcers are a common complication of SCD and increase in occurrence with advancing age. By their fourth decade of life, 22% of patients with HbSS and 9% of patients with HbSC will report a history of leg ulcers.[62] Standard treatment of leg ulcers is debridement, wet to dry dressings, topical agents, and prompt treatment of soft tissue infection and/or osteomyelitis.[15] There have been anecdotal reports of transfusion stimulating ulcer healing. Although there are no studies to support chronic transfusion therapy for long-term management, RBC transfusion may be beneficial for patients undergoing surgical debridement, skin grafts, or muscle flaps to promote healing.[63]

### *Vasoocclusive Crisis*

Acute VOC is the most common cause of hospital admissions among patients with SCD. In the Cooperative Study of SCD, mean frequencies of pain episodes for patients with HbSC or HbSβ+, HbSS, and HbSβ° were 0.4, 0.8, and 1.0 episodes per year, respectively.[64] The average hospital stay for VOC is 7.5 days for adults and 4.4 days for children. Treatment of severe VOC requiring hospitalization is pain management with nonsteroidal antiinflammatory drugs and parenteral opioids, intravenous (IV) hydration, and incentive spirometry to minimize the risk of ACS. During acute uncomplicated VOC, mild exacerbation of anemia is common but does not require transfusion. There are no data to support RBC transfusion to manage acute uncomplicated VOC, and transfusion in this setting is associated with a higher risk of RBC alloimmunization.[65] A subset of patients have unusually frequent and severe pain episodes, associated with a poor quality of life. There is empirical evidence that chronic transfusions may reduce acute painful episodes,[11,66] but a concurrent multidisciplinary pain program and periodic assessment for treatment response is required.

### *Priapism*

Priapism affects approximately 35% of boys and men with SCD.[67] Prolonged and recurrent episodes of priapism are associated with tissue necrosis and fibrosis leading to erectile dysfunction. Initial management consists of IV fluids and analgesics; subsequent interventions include penile aspiration and corporal irrigation using $\alpha$-adrenergic agents. The use of oral pseudoephedrine and low-dose phosphodiesterase type 5 inhibitors has been reported to have prophylactic benefit in SCD-associated priapism, and limited experience suggests hydroxyurea may prevent recurrence.[68] Surgical shunting procedures and penile prosthesis implantation are used when conservative measures fail.[69]

The benefit of RBC transfusion for acute priapism in SCD is controversial. A systematic literature review of patients with SCD-associated priapism reported a mean time to detumescence of 8.0 days in 16 patients who did not receive transfusion compared with 11 days in 26 individuals who received transfusion. The review identified 9 cases of serious neurologic sequelae, including obtundation, seizures, and stroke following transfusion consistent with *A*ssociation of *S*ickle cell disease, *P*riapism, *E*xchange transfusion, and *N*eurologic events (ASPEN) syndrome. Most resolved completely but left severe neurologic deficits in some.[70] Given the risk of ASPEN, blood transfusion is not typically recommended to treat acute priapism in patients with SCD. Chronic transfusion therapy is sometimes used to prevent recurrent intermittent priapism, but there is no published evidence of its efficacy. The NHLBI-appointed SCD expert panel recommends against the use of transfusion for the treatment of priapism.[15] **Table 1** summarizes indications for and against transfusion therapy in patients with SCD.

## PREVENTION OF COMPLICATIONS

### *Alloimmunization*

RBC alloimmunization is a major complication associated with transfusions in SCD. Alloantibodies to the Rh (primarily C and E) and Kell (typically K) systems compose more than two-thirds of the antibodies detected. The high rate of alloimmunization is multifactorial, but discordance of blood group antigen expression on donor and patient RBCs is likely the major contributing factor. Prevention has focused on prophylactic RBC antigen matching, either limited C, E, K matching or extended antigen matching to include the Duffy, Kidd, and MNS systems ($Fy^a$, $Fy^b$, $Jk^a$, $Jk^b$, S). Alloimmunization prevalence in patients with SCD ranges from 27% to 75% with ABO-D matching alone, 5% to 14% with limited C, E, and K matching, and 0% to 7% for extended RBC antigen matching (**Table 2**). The rate of alloantibody formation ranges from 1.7 to 3.9 antibodies formed per 100 units transfused with ABO-D matching, 0.26 to 0.50 with limited C, E, K matching, and 0 to 0.10 with extended antigen matching (see **Table 2**).

Limited C-, E-, and K-matched RBCs can reduce alloimmunization (see **Table 2**). Despite consensus in the United States to provide C-, E-, and K-matched RBCs for patients with SCD,[15] this has not been universally practiced.[71,72] Some transfusion services provide extended matched RBCs after patients with SCD have formed one alloantibody, recognizing these patients as "immune responders."[73] In addition to C-, E-, and K-matched RBCs, recruitment of dedicated donors to limit donor exposure for a given patient[74] or providing RBCs from African American donors who are more likely to have similar Jk, Fy, or S antigen status[75] have been alternative strategies used for SCD. In a single-institution study, C-, E-, and K-matched RBCs from African American donors resulted in no cases of anti-K formation and a low rate of anti-Jk, -Fy, and -S antibodies; but Rh immunization remained problematic (**Fig. 1**).[75]

**Table 2**
**Red blood cell antigen matching and alloimmunization**

| Study | N | Total Units Transfused | Matching | Patients with Alloantibodies (%) | Rate (Alloantibody per 100 Units) |
|---|---|---|---|---|---|
| Ambruso et al,[87] 1987 | 12 | 492 | ABO, D | 75 | 3.5 |
| Rosse et al,[88] 1990 | 1044 | n/a | ABO, D | 27 | n/a |
| Vichinsky et al,[89] 1990 | 107 | 1711 | ABO, D | 30 | 3.9 |
| Aygun et al,[90] 2002 | 140 | 3239 | ABO, D | 37 | n/a |
| Castro et al,[91] 2002 | 351 | 8939 | ABO, D | 29 | n/a |
| Sakhalkar et al,[92] 2005 | 387 | 14,263 | ABO, D | 31 | 1.7 |
| Vichinsky et al,[93] 2001 | 61 | 1830 | Limited (C, E, K) | 11 | 0.50 |
| Sakhalkar et al,[92] 2005 | 113 | 2354 | Limited (C, E, K) | 5 | 0.26 |
| O'Suoji et al,[94] 2013 | 180 | n/a | Limited (C, E, K) | 14 | n/a |
| DeBaun et al,[44] 2014 | 90 | 3236 | Limited (C, E, K) | 4.5 | 0.28 |
| Tahhan et al,[95] 1994 | 40 | 608 | Extended matching[a] | 0 | 0 |
| Lasalle-Williams et al,[96] 2011 | 99 | 6946 | Extended matching[b] | 7 | 0.10 |
| Chou et al,[75] 2013 | 182 | 44,482 | Limited (C, E, K) from African American donors | 44 | 0.33 |

*Abbreviation:* n/a, not available.
[a] C/c, E/e, K, Fya, Fyb, S.
[b] C/c, E/e, K, Fya, Jka, Jkb.
*Data from* Refs.[44,75,87–96]

Inheritance of variant *RHD* and *RHCE* genes encoding amino acid changes in the Rh antigens (D, C, c, E, e) is common in Africans, and its contribution to alloimmunization in patients with SCD despite Rh-matching programs has been increasingly appreciated.[75,76] Many *RH* variants encode partial Rh antigens, and individuals become immunized when exposed to epitopes that their own cells lack.[75,77] *RH* alleles that encode altered D, C, and e antigens often underlie the complex Rh alloantibody and apparent autoantibody specificities found in patients with SCD. Patients form anti-D, -C, and/or -e despite their own RBCs testing positive for those antigens and may represent Rh alloantibodies rather than autoantibodies. These antibodies can be clinically significant, and future transfusions should be with antigen-negative RBCs. This requirement poses significant challenges to transfusion services in providing compatible RBCs to these patients, taking care to avoid additional alloantibody development.

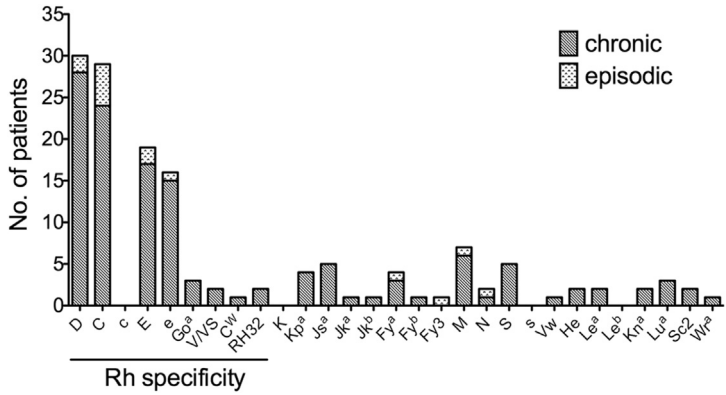


**Fig. 1.** Antibody specificities in patients with SCD transfused with Rh D-, C-, E-, and K-matched RBCs from African American donors. One hundred forty-six specific antibodies in 123 chronically and 59 episodically transfused patients identified at a single institution over 15 years. (*From* Chou ST, Jackson T, Vege S, et al. High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. Blood 2013;122(6):1064; with permission. Copyright © the American Society of Hematology.)

Patients with SCD benefit from having an extended RBC antigen phenotype (C/c, E/e, K/k, $Fy^a/Fy^b$, $Jk^a/Jk^b$, M/N, S/s, and $Le^a/Le^b$) completed in the first year of life. Knowledge of RBC antigen status facilitates antibody evaluation and identification of compatible RBC units in patients with a newly formed antibody. RBCs should be matched for C, E, and K antigens at a minimum.[15] Extended antigen-matched RBCs to minimize alloimmunization against Kidd, Duffy, and S antigens is preferable; but finding sufficient RBC units for chronically transfused patients may be challenging for some regions. Overall transfusion cost increases with higher levels of antigen matching, which is prohibitive for many providers. Using molecular blood typing can augment serologic typing and may allow the ability to provide highly antigen-matched products in the future and potentially be cost saving.[78,79]

Altered *RH* alleles in patients with SCD suggest an important emerging role for molecular methods to improve RBC matching in the Rh system.[75,80] Prevention of Rh alloantibody formation in patients with partial antigens is a challenge. Providing antigen-negative RBCs for individuals predicted to exclusively express partial Rh antigens may be performed on an individual case basis, with consideration of their extended RBC antigen profile, alloimmunization history and specificities, and the predicted availability of appropriate donors. For individuals with the relatively common hybrid *RHD*DIIIa-CE(4–7)-D* gene that encodes a partial C antigen, providing C-negative RBCs to those lacking an *RHCE* gene encoding conventional C can minimize anti-C alloimmunization and is consistent with a prophylactic C matching policy.[81] For patients whose *RH* genotypes predict exclusive expression of partial D and/or e antigens, selection of appropriate RBC units is more complex. For example, D-negative units are more likely to be identified among European donors. Providing D-negative RBCs to patients with partial D antigen status may increase alloimmunization risk to other antigens (Fya, Jkb, and S) that are more common in Europeans compared with Africans. As sequencing platforms increasingly improve and become cost-effective, *RH* genotyping can complement serologic testing for both typing and matching donors and patients.

### *Monitoring and Treatment of Iron Overload*

Patients with SCD on chronic or recurrent episodic transfusions are at risk for iron overload and subsequent liver, endocrine, and/or cardiac dysfunction.[82] Recommendations for monitoring and treatment of iron overload in SCD are largely based on thalassemia literature. Transfusional iron burden should be monitored with serum ferritin levels and liver and cardiac MRI. Liver iron quantification by R2 and R2* MRI techniques correlates well with liver iron content (LIC) determined by liver biopsy.[83] Although less common than comparably transfused patients with thalassemia major, cardiac iron overload occurs in a small proportion of patients with SCD with exceptionally poor control of iron status.[84] In such patients, cardiac T2* MRI can predict the risk of developing heart disease, allowing intensification of therapy.[85] LIC should be measured by R2-MRI every 1 to 2 years while on chronic transfusions and/or if serum ferritin remains greater than 1000 ng/mL. Iron-chelating agents are typically initiated within 1 to 2 years of instituting chronic transfusions, after 10 to 20 cumulative RBC units (~120 mL/kg), or when LIC is 7 mg/g or greater dry weight.[86] Chelation is titrated to maintain serum ferritin less than 1000 ng/mL and LIC less than 7 mg/g liver dry weight, extrapolated from the thalassemia data.[2]

Iron chelation therapy can maintain a negative iron balance in most compliant patients requiring chronic transfusions. Deferoxamine (25–40 mg/kg/d SQ) and deferasirox (20–40 mg/kg/d by mouth) have been licensed for the treatment of iron overload in SCD, but the safety and efficacy of deferiprone (75–100 mg/kg/d by mouth) has not been established for SCD in the United States. Although deferiprone has been available for patients with SCD outside the United States and Canada since 1995, experience is limited.[2,82]

Unique to SCD, the iron-loading rate of transfusion therapy depends on the modality used (simple vs exchange), the type of exchange (partial manual vs automated), and the target Hb and percentage of HbS.[82] The net iron balance is also influenced by dose and compliance with iron chelation therapy. Patients with severe iron overload may benefit from erythrocytapheresis combined with chelation and by adjusting automated erythrocytapheresis parameters to achieve minimal iron loading. **Tables 3** and **4** provide calculations of transfusion-associated iron accumulation and balance with different transfusion regimens.

**Table 3**
**Calculations of iron accumulation from transfusion**

| RBC Transfusion Volumes | Amount of Fe Accumulation |
|---|---|
| 1 mL of erythrocytes | Approximately 1 mg of Fe |
| Fe content of transfused blood | Approximately 0.75 mg/mL (225 mg Fe per 300 mL unit)[a] |
| Approximately 2 units of RBCs | Approximately 0.5 g of Fe accumulation within the body[b] |
| 10 mL/kg of RBCs | Approximately 7.5 mg Fe/kg |
| 15 mL/kg of RBCs | Approximately 11.3 mg Fe/kg |
| For chronic transfusions | |
| 10 mL/kg RBCs every 4 weeks | Approximately 0.25 mg/kg/d |
| 15 mL/kg RBCs every 4 weeks | Approximately 0.40 mg/kg/d |
| 15 mL/kg RBCs every 3 weeks | Approximately 0.54 mg/kg/d |

*Abbreviation:* Fe, iron.
[a] This value assumes a red cell unit hematocrit of 65%.[6]
[b] Adults normally have approximately 4 to 5 g of total body iron.

**Table 4**
**Iron balance with transfusion regimens**

| Transfusion Modality | Fe Accumulation (mg/kg/d)[a] | DFX Dosage to Balance Input | DFO Dosage to Balance Input |
|---|---|---|---|
| Simple transfusion | | | |
| Target HbS <30% | 0.42 | 20 mg/kg/d | 40 mg/kg × 5/wk |
| Target HbS <50% | 0.32 | 16 mg/kg/d | 32 mg/kg × 5/wk |
| Partial Manual Exchange[b] | | | |
| Target HbS <30% | 0.36 | ~18 mg/kg/d | 37 mg/kg × 5/wk |
| Erythrocytapheresis | | | |
| Target HbS <30% | 0.04–0.08 | <5 mg/kg/d | <10 mg/kg × 5/wk |
| Target HbS <50% | ≤0.052 | <5 mg/kg/d | <10 mg/kg × 5/wk |

*Abbreviations:* DFO, deferiprone; DFX, deferoxamine; Fe, iron.

[a] These calculations are approximations. The rate of iron accumulation varies within the transfusion modality used based on transfusion volume (10 vs 15 mL/kg), frequency of transfusions (every 3 weeks vs every 4 weeks), phlebotomy volume (partial manual exchange), and after exchange target Hb (erythrocytapheresis).

[b] Fe accumulation approximation for partial manual exchange extrapolated from data calculations from reference.[6]

*Adapted from* Porter J, Garbowski M. Consequences and management of iron overload in sickle cell disease. Hematology Am Soc Hematol Educ Program 2013;2013:448.

## SUMMARY

RBC transfusion is a critical component in the treatment of SCD. Clinicians should be knowledgeable of evidence-based or expert panel–based consensus of transfusion indications and strategies to prevent and manage transfusion-related complications.

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