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Transfusion support in patients with sickle cell disease ☆

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ABSTRACT

Blood transfusions are an integral component of the management of acute and chronic complications of sickle cell disease. Red cells can be administered as a simple transfusion, part of a modified exchange procedure involving manual removal of autologous red cells and infusion of donor red cells, and part of an automated red cell exchange procedure using apheresis techniques. Individuals with sickle cell disease are at risk of multiple complications of blood transfusions, including transfusional hemosiderosis, auto- and alloimmunization to minor red cell and human leukocyte antigens, delayed hemolytic transfusion reactions, and hyper-hemolysis. In low- and middle-income countries in sub-Saharan Africa, where a directed donor system is prevalent and limited laboratory methods are in place to perform extended red cell phenotyping, leukodepletion of cellular products, and infectious disease screening, there are additional challenges to providing safe and adequate transfusion support for this patient population. We review current indications for acute and chronic transfusions in sickle cell disease that are derived primarily from randomized controlled trials and observational studies in children living in high-income countries. We will highlight populations with unique transfusion needs, such as pregnant women and children, as well as the role of the transfusion medicine consultative service for individuals with sickle cell disease planning to have curative hematopoietic stem cell transplantation or gene therapy. Finally, we will discuss risk factors for alloimmunization in individuals with sickle cell disease, emerging new strategies to prevent alloimmunization in this population, and critical gaps in the implementation of transfusion guidelines for sickle cell disease in high- and low-income countries.

Introduction

Sickle cell disease (SCD) is an inherited blood disorder due to a point mutation in the beta globin gene, resulting in the production of insoluble sickle hemoglobin [1]. Numerous complications of vaso-occlusion can occur in affected individuals, including but not limited to recurrent acute pain episodes, silent cerebral infarcts and stroke, priapism, pigmentary cholelithiasis, functional asplenia secondary to repeated splenic infarcts and avascular necrosis [2]. Blood transfusion therapy is integral for the management of several acute and chronic complications of SCD [3]. Red blood cell (RBC) transfusions can be administered as a simple transfusion (infusion of donor RBCs), modified exchange transfusion that entails manual removal of autologous whole blood and infusion of donor RBC, and automated red cell exchange using apheresis methods (erythrocytapheresis). Although blood transfusion therapy can decrease SCD-related morbidity, it is associated with a number of risks, including alloimmunization, transfusional hemosiderosis, delayed hemolytic transfusion reactions, hyperhemolysis, and sensitization to donor human leukocyte antigens (HLAs) prior to curative hematopoietic stem cell transplantation [4]. In this review, we will discuss the current benefits, risks, and indications of blood transfusion therapy for the management of children and adults with SCD. We will also highlight opportunities for improvement in the administration of blood products for individuals with SCD, with a focus on emerging strategies to reduce the risk of alloimmunization.

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Table 1
Advantages and disadvantages of current transfusion strategies for individuals with sickle cell disease

	Simple transfusions	Modified exchange transfusions	Automated red cell exchange (erythrocytapheresis)
Advantages	- Easiest to perform (does not require apheresis machine) - Requires minimal skilled personnel - Least costly - Can use peripheral or central access	- Lowers HbS more effectively than simple transfusions - Lower risk of hyperviscosity than simple transfusions - Lower risk of excessive iron stores than simple transfusions	- Quickest to perform - Allows for longer intervals between procedures - Most efficiently lowers HbS levels -May have additional benefits with respect to transient reduction of pro-inflammatory markers and reduction of alloimmunization risk - Can maintain net even or negative iron stores - Lowest risk of hyperviscosity
Disadvantages	- Highest risk of excessive iron stores and hyperviscosity - Least efficient method to lower HbS - Takes the longest to perform	- Higher risk of excessive iron stores and hyperviscosity than automated red cell exchange transfusions - Increased risk of vasovagal and phlebotomy-related complications during manual autologous red cell removal phase - Does not lower HbS level as effectively as automated red cell exchange	- Risk of machine malfunction (i.e. return of autologous red blood cells to patient) - Requirement for skilled nursing and costly apheresis machines - Some centers require central venous access - Cost limits availability at many care centers - Increased donor red blood cell exposure

Abbrevations: HbS = hemoglobin S

Transfusion approaches in SCD

RBC transfusions are integral in the management of complications of SCD, using either single transfusion episodes for acute complications such as acute chest syndrome, or as part of a regular long-term transfusion program to prevent progression of complications of SCD [5]. Regardless of the strategy, the overall goal is to increase oxygenation of distal tissues while minimizing vaso-occlusive complications of SCD, in part by diluting sickled RBCs and improving vascular perfusion. We have summarized each approach and associated advantages and disadvantages in Table 1. No randomized controlled trials have directly compared each of these three blood transfusion strategies with regards to safety and efficacy for the prevention of vaso-occlusive complications. The selection of strategy depends on several patient and health care system-related factors, including cost, venous access, institutional expertise and iron stores.

Simple transfusions

Simple transfusions are advantageous because they do not require skilled nursing personnel or equipment, and can be performed using peripheral venous access in most health care settings [6]. Typical dosing is 10–15 mL/kg of red cells for pediatric patents, and 1–2 units for adults, depending on the starting hemoglobin. The typical response is 1–2 g/dL of hemoglobin rise, depending on the anticoagulant/preservative solution (citrate phosphate dextrose adenine (CPDA) versus AS-1, 3, 5), as well as baseline hemolysis in the recipient of the blood product. However, compared to other methods for red cell transfusion, simple transfusions have the highest risk of hyperviscosity and excessive iron stores, and they are the least effective method for reducing hemoglobin S (HbS) levels. Serious adverse events occur with transfusion in SCD, and caution must be exercised to avoid over transfusion [7-9].

Serial monitoring of ferritin levels and initiation of chelation therapy as needed to prevent or treat transfusional hemosiderosis is an essential component of management for individuals with SCD who are receiving chronic simple transfusions. Treatment for transfusional hemosiderosis should start when patients who are over 2-years of age have received approximately 10 transfusions, have a serum ferritin >1000 µg/L, or liver iron content >3 mg/g dry weight liver [7]. In high-income countries, T2* magnetic resonance imaging or superconducting quantum interference device can be used to monitor body iron stores and guide chelation therapy [10].

Modified exchange transfusions

Modified exchange transfusion (also known as partial or manual exchange transfusion) entails removal of autologous whole blood, followed by infusion of sickle negative donor RBCs [8]. The volume of red cells removed often depends on the preprocedural hemoglobin level, although practice is not standardized across institutions, with further efforts to minimize blood loss via phlebotomy in patients with recent stroke [9,10]. Modified exchanges are not as effective as automated red cell exchange transfusions for lowering HbS levels and minimizing the risk of hyperviscosity and excessive iron stores. However, modified exchange transfusions are less costly and more widely available than are automated red cell exchange transfusions, as they do not require skilled apheresis nursing personnel or apheresis machines. Therefore, modified red cell exchange transfusions are used in resource-constrained settings in which performing automated red cell exchange is not feasible. This approach has been used for the prevention of recurrent cerebral infarcts with a favorable safety profile [11].

Automated red cell exchange transfusions

Automated red cell exchange transfusions, also referred to as erythrocytapheresis, achieves HbS targets quickly and more consistently, while minimizing the risk of hyperviscosity and excessive iron stores [12]. However, there are no comparative studies, in either the pediatric or the adult setting, between automated and manual red cell exchange. Despite the increased dose of donor RBCs, automated red cell exchange transfusions reduce the risk of delayed hemolytic transfusion reactions and alloimmunization when compared to simple transfusions [13-16]. The etiology of this seemingly paradoxical decrease in alloimmunization rates with automated red cell exchange transfusions is not entirely clear, although some experts speculate that removal of leukocytes, cytokines, and other pro-inflammatory proteins from patient plasma during the procedure may reduce the propensity for auto- and alloantibody formation [13]. This theory is further supported by studies demonstrating that the risk of alloantibody formation in SCD is highest during acute inflammatory events [17-20], as shown in a study of 8 individuals with SCD and acute chest syndrome that demonstrated a reduction in white blood cell count, absolute neutrophil count, platelet count and soluble vascular adhesion molecule-1 (sVCAM-1) immediately following automated red cell exchange [21]. In spite of the multiple advantages of automated red cell exchange over simple and modified exchange transfusion strategies, cost, and requirement for skilled apheresis nursing and machines are tremendous barriers to its widespread availabil-

ity. Additionally, some centers require central venous access to perform automated red cell exchange transfusions to maintain a high rate of blood flow, which further limits the feasibility of this approach.

Isovolemic hemodilution preceding automated red cell exchange transfusions

Isovolemic hemodilution using normal saline preceding automated red cell exchange transfusions in individuals with SCD has been described in a single-center study with a favorable safety profile for secondary stroke prevention [22,23]. During the initial isovolemic hemodilution phase, which was performed on 20 individuals over a 7-year period with a weight of at least 25 kg and hematocrit (Hct) of at least 23, the patient's red cells were removed and replaced with normal saline to achieve a pre-defined Hct. This innovative strategy for chronic transfusion therapy in SCD was associated with cost savings of $4.5 million over 10 years due to an increased interval between red cell exchange procedures from 37 to 53 days, and an 11% reduction in red cell utilization attributable to the isovolemic hemodilution phase [22]. Currently, isovolemic hemodilution preceding automated red cell exchange transfusions is not widely practiced due to limited familiarity with this technique and concerns about increased risk of vaso-vagal reactions and cerebral hypoperfusion related to iatrogenic acute anemia.

Laboratory goals for chronic transfusion therapy

In acute situations, such as acute stroke or severe acute chest syndrome, automated red cell exchange transfusions using apheresis methods are preferred primarily because of their ability to rapidly lower the HbS level. Although there are no high quality studies to support achieving specific laboratory goals following RBC exchange, typically a HbS of 30–40% or lower [6,24] and hemoglobin of 9–10 g/dL are targeted [6,25]. However, data suggest that even in chronically transfused children with SCD, lowering the HbS level below 30% and as low as 10% does not effectively prevent recurrent cerebral infarcts in all individuals [26]. Therefore, studies to evaluate alternative laboratory targets to monitor the efficacy of chronic transfusion therapy for the prevention of vaso-occlusive complications are warranted.

Indications for red blood cell transfusions in SCD

Transfusions are used in clinical practice to manage multiple acute and chronic complications of SCD, with varying degrees of evidence. The evidence to support transfusion therapy for primary and secondary stroke prevention in SCD is the strongest. We have summarized consensus-based guidelines for blood transfusion therapy for SCD in the acute and chronic settings in Table 2.

Transfusion support for stroke in sickle cell disease

Acute stroke: Neurological complications of SCD, including stroke and silent cerebral infarcts, have debilitating clinical sequelae [27]. For children and adults with SCD presenting with acute stroke, automated red cell exchange transfusion is associated with a lower risk of recurrent stroke when compared to simple transfusion [6]. The immediate goals of transfusion therapy are to increase cerebral perfusion and oxygenation, and to ultimately prevent the progression of further cerebral infarcts.

Primary and secondary stroke prevention: The role of chronic transfusion therapy for primary and secondary stroke prevention in SCD is well defined. The supporting literature for primary stroke prevention in SCD applies only to children and adolescents. Expert guidelines recommend that children with two transcranial Doppler velocity measurements $\geq$ 200 cm/s measured within a 1–2 week period should undergo automated red cell exchange transfusions approximately every 3–6 weeks for primary stroke recommendation [28,29]]. Typically, the HbS goal is $\leq$30% and the hemoglobin is targeted to 9 to 10 g/dL [6]. Several randomized controlled trials of children with SCD have demonstrated a benefit of chronic transfusion therapy over observation for primary stroke prevention [30,31], secondary prevention of silent cerebral infarcts and stroke [31,32], as well as a higher rate of strokes when transfusions are discontinued [33,34]. Of note, all the randomized controlled trials demonstrating a benefit of chronic transfusion therapy for primary or secondary stroke prevention have been performed in children, despite the very high rate of recurrence of cerebral infarcts in adults [35]. In the absence of high quality data, the consensus in the hematology and transfusion medicine communities has been to extrapolate data from the pediatric literature, and initiate chronic transfusion therapy for secondary prevention of silent cerebral infarcts and stroke in adults with SCD.

Emergent transfusion for acute chest syndrome

Transfusion therapy is commonly accepted as a management strategy for acute chest syndrome. Simple and automated exchange transfusions have been shown to improve clinical outcomes, oxygenation, and radiographic findings for individuals with SCD and acute chest syndrome [36,37]. A retrospective review of 53 episodes of acute chest syndrome in 44 children and adolescents with SCD demonstrated improvement in respiratory distress, as measured by the Clinical Respiratory Score, within a 24-hour period [38]. The results of retrospective studies comparing simple transfusions to automated exchange transfusions for acute chest syndrome have been inconclusive [39], and no randomized controlled trials have been performed to compare the relative benefits of both approaches.

Transfusion for management of acute vaso-occlusive pain episodes

Acute vaso-occlusive pain episodes: There are no high quality data to support the use of simple transfusions to manage uncomplicated acute vaso-occlusive pain episodes in children and adults with SCD [29,40,41]. A pilot study of transfusion therapy for the management of acute vaso-occlusive pain within 24 hours of admission did not demonstrate any benefit of transfusion therapy in terms of length of hospital stay, total opioid use, and mean pain score 48 hours after transfusion [42]. Another review of 39,324 admissions of 4,348 adults with SCD who were admitted from 2007 to 2012 for acute vaso-occlusive pain showed a reduction in mortality and 30-day readmission rate in those receiving inpatient transfusions [43]. However, many of the patients included in this study had other indications for transfusion that were unrelated to pain. Chronic transfusions may prevent acute pain episodes in part by lowering HbS levels, thereby decreasing vaso-occlusive events and ischemic-reperfusion injury. In pediatric randomized controlled trials for primary stroke prevention, chronic transfusion therapy had a clear benefit in terms of reducing recurrent acute pain episodes compared to standard therapy [31,44]. Compared to hydroxyurea, chronic transfusions have also been shown to be more effective in preventing recurrent severe acute pain episodes [45,46].

Recurrent pain events or chronic pain: Chronic transfusion therapy has been shown to ameliorate frequent pain events in individuals with SCD [54,55]. However, there are limited studies supporting the efficacy of this approach. Available data suggest that patients on hydroxyurea, even when participating in well-designed

Table 2
Indications and contraindications for blood transfusions in sickle cell disease

Acute indications for transfusion in sickle cell disease			
	Notes	Quality of Evidence	Reference(s)
Acute stroke	Emergent automated red cell exchange transfusion is recommended for children and adults with sickle cell disease and acute stroke in order to improve cerebral oxygenation and prevent progressive ischemic injury to the brain	Category 1: Apheresis is accepted as first line therapy Grade 1C: Strong recommendation based on low quality evidence Moderate recommendation based on low quality evidence	American Society for Apheresis (AFSA) Guidelines 2016[1] NHLBI Expert Panel Report 2014[2]
Acute chest syndrome	Simple transfusion is recommended for symptomatic acute chest syndrome when the hemoglobin is $\geq$ 1 g/dL below baseline Automated red cell exchange transfusion is recommended for severe symptomatic acute chest syndrome (oxygen saturation $<$ 90% despite supplemental oxygen therapy) Automated red cell exchange transfusion is recommended for severe acute chest syndrome	Weak recommendation based on low quality evidence Strong recommendation based on low quality evidence Category II: Apheresis is accepted as second-line therapy Grade 1C: Strong recommendation based on low quality or very low quality evidence	NHLBI Expert Panel Report 2014[2] NHLBI Expert Panel Report 2014[2] American Society for Apheresis (AFSA) Guidelines 2016[1]
Acute multisystems organ failure	Emergent automated red cell exchange transfusion is recommended based on benefit demonstrated in observational studies	Category III: Optimum role for apheresis not established; decision making should be individualized Grade 2C: Weak recommendation based on low quality or very low quality evidence	American Society for Apheresis (AFSA) Guidelines 2016[1]
Intrahepatic cholestasis	Emergent automated red cell exchange transfusion is recommended based on benefit demonstrated in observational studies	Category III: Optimum role for apheresis not established; decision making should be individualized Grade 2C: Weak recommendation based on low quality or very low quality evidence	American Society for Apheresis (AFSA) Guidelines 2016[1]
Hepatic/ splenic sequestration	Emergent automated red cell exchange transfusion is recommended based on benefit demonstrated in observational studies	Category III: Optimum role for apheresis not established; decision making should be individualized Grade 2C: Weak recommendation based on low quality or very low quality evidence	American Society for Apheresis (AFSA) Guidelines 2016[1]
Priapism	No clear benefit	Category III: Optimum role for apheresis not established; decision making should be individualized Grade 2C: Weak recommendation based on low quality or very low quality evidence Moderate recommendation based on low quality evidence	American Society for Apheresis (AFSA) Guidelines 2016[1] NHLBI Expert Panel Report 2014[2]
Chronic indications for transfusion in sickle cell disease			
	Notes	Quality of Evidence	Reference(s)
Primary stroke prevention	Multiple randomized controlled trials in children and adolescents with sickle cell disease support the use of chronic transfusions for primary stroke prevention when transcranial Doppler velocities are $\geq$ 200 cm/sec[3, 4]. There are no data to support chronic transfusions for primary stroke prevention in adults with sickle cell disease.	Strong recommendation, based on high quality evidence	NHLBI Expert Panel Report 2014[2]]
Secondary stroke prevention	Randomized controlled trials in children and adolescents with sickle cell disease support the use of chronic transfusion therapy for secondary prevention of cerebral infarcts and strokes[4, 5]. While there are no high quality data to support the use of chronic transfusion therapy for secondary stroke prevention in adults with sickle cell disease, this is accepted standard practice due to the high risk of stroke recurrence in the adult population.	Moderate recommendation based on low quality evidence Category 1: apheresis is accepted as first line therapy Grade 1A: strong recommendation based on high quality evidence	NHLBI Expert Panel Report 2014[2] American Society for Apheresis (AFSA) Guidelines 2016[1]
Perioperative setting	For children and adults with sickle cell disease undergoing surgery requiring general anesthesia, transfuse to raise the hemoglobin level to 10 g/dL For individuals with sickle cell anemia (HbSS) with a hemoglobin level of $\geq$ 8.5 g/dL without transfusion, on chronic hydroxyurea or undergoing high risk surgery, consult a hematology expert for the appropriate transfusion method For individuals with HbSC or HbSβ+thalassemia, consult a hematologist to determine if partial or full exchange transfusion therapy is indicated before a surgical procedure involving general anesthesia	Strong recommendation, moderate quality evidence Strong recommendation, low quality evidence Moderate recommendation, low quality evidence	NHLBI Expert Panel Report 2014[2] NHLBI Expert Panel Report 2014[2] NHLBI Expert Panel Report 2014[2]
Pregnancy	Studies have demonstrated a reduction in recurrent acute pain events in pregnant women with sickle cell disease receiving prophylactic transfusion therapy, with conflicting evidence about its effect on maternal and fetal morbidity and mortality[6-8]	Although there are no official expert guidelines in the United States, it is accepted standard of care practice to initiate prophylactic transfusions for pregnant women who experience recurrent severe acute pain episodes	

(*continued on next page*)

Table 2 (*continued*)

Recurrent acute pain episodes refractory to hydroxyurea therapy	Multiple pediatric randomized controlled trials for primary and secondary stroke prevention have shown a benefit of chronic transfusion therapy for the reduction of recurrent severe acute pain episodes when compared to either standard care therapy or hydroxyurea[4, 9-11]	There are no official guidelines at this time that recommend the use of chronic transfusion therapy for recurrent acute pain episodes refractory to hydroxyurea therapy, although this is standard of care at multiple academic centers with expertise in sickle cell disease management
Contraindications to transfusion in sickle cell disease		
	Notes	Reference(s)
Acute vaso-occlusive pain episodes	Blood transfusions should not be administered for the management of acute vaso-occlusive pain episodes in sickle cell disease due to lack of supporting evidence	NHLBI Expert Panel Report 2014 Guidelines on red cell transfusion in sickle cell disease part II: indications for transfusion Best practices for transfusion for patients with sickle cell disease [2, 12, 13]
Asymptomatic anemia	Individuals with sickle cell disease should not receive simple transfusions for strict hemoglobin cut offs if their hemoglobin levels are within their baseline range and there is no other acute indication for transfusion	NHLBI Expert Panel Report 2014[2]

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clinical trials, may continue to frequently utilize health care facilities [56]. In the phase II study of crizanlizumab for adults with SCD with 2–10 acute vaso-occlusive pain episodes per year, 40 patients randomized to placebo and hydroxyurea developed a median of 3.58 acute vaso-occlusive pain episodes per year while on study, higher than their baseline rate of 2.98 pain episodes per year [57]. Hilliard et al showed that chronic transfusion therapy for one year significantly reduced the number of total emergency room visits for pain (6 vs 2.5 pain visits/year, $P = .005$), mean hospitalizations for pain (3.4 vs 0.9 pain admissions/year), and mean hospital days per year for pain episodes (23.5 vs 4.5, $P = .0001$), compared with 1 year prior to initiation of transfusion therapy. Notably, no significant difference in opioid prescription patterns was observed during the year of transfusion therapy [58]. Currently, the role of chronic transfusions for individuals with SCD and chronic pain remains unclear.

Transfusion support for other acute complications of SCD

Severe acute anemia: Individuals with SCD who are symptomatic from their anemia should receive a simple transfusion, as well as those with acute stroke or acute chest syndrome who are acutely anemic and might need to wait several hours before undergoing an automated red cell exchange. Most patients with SCD have chronic anemia, with a baseline hemoglobin in the range of 7.0 to 11.0 g/dL [47]. Simple transfusions should not be given to asymptomatic individuals with SCD when their hemoglobin level is within a phenotypically acceptable reference range or within <2 g/dL of their individual baseline [60]. Not only is there a lack of evidence to support the practice of using a firm hemoglobin cut off for transfusion, but transfusions in this patient population have serious risks, including auto- and alloimmunization to minor red cell antigens, hyperviscosity, transfusion-associated hemochromatosis, exposure to donor HLAs, and delayed hemolytic transfusion reactions.

Acute priapism: There are no randomized controlled trials demonstrating a benefit of automated red cell exchange transfusions for the management of acute priapism, although exchange transfusions have been advocated as a salvage therapy when other treatments, such as analgesia, α-adrenergic agents, and penile aspiration or irrigation fail in the acute setting. A review of 42 case reports showed no improvement in time to detumescence with blood transfusion therapy (mean of 10.8 days) when compared to conventional therapy (mean of 8.0 days), and adverse neurological sequelae were described in 9 individuals who received blood transfusion therapy [48]. It is unclear whether the neurological sequelae observed in this study were related to the targeted high post-transfusion hemoglobin levels, resulting in hyperviscosity. Another single institution study of 239 automated red cell exchanges for refractory acute priapism over a 15-year period did not report any neurological or other adverse sequelae [49].

Prophylactic perioperative transfusion

The stress of surgical procedures and exposure to general anesthesia are risk factors for vaso-occlusive events in individuals with SCD, including acute pain episodes, stroke, and acute chest syndrome. In the largest, prospective study of children and adults with SCD, the Cooperative Cohort Study of Sickle Cell Disease (CSSCD), acute vaso-occlusive complications occurred in 18.6% of individuals, and 12 deaths occurred in 1079 cases [29,50]. The Transfusion Alternatives Preoperatively in sickle Cell Disease (CSSCD) randomized 67 individuals in Canada and Europe with SCD to either no preoperative transfusion or preoperative transfusion who were undergoing low- or intermediate-risk procedures, with a goal hemoglobin of 10 g/dL [51]. The study demonstrated a benefit of pre-operative transfusion for individuals undergoing medium-risk surgery and was terminated early. Another randomized controlled trial compared pre-operative simple transfusion, with a goal hemoglobin of 10 g/dL to automated red cell exchange transfusion, with a goal HbS level $<$30%, with no statistically significant difference in perioperative complications between both arms [52]. Similarly, in a study of 39 children with SCD undergoing adenotonsillectomy, 30% of patients experienced complications ranging from mild infection to acute chest syndrome, and there was no difference in the rate of complications between those receiving simple transfusions with a goal hemoglobin of 10 g/dL, versus those receiving automated red cell exchanges with a goal HbS level $<$30% [53]. In another study of 46 individuals with SCD there was no benefit in terms of reduction in perioperative acute vaso-occlusive pain episodes and acute chest syndrome between those who receiving pre-operative simple transfusions, automated exchange transfusions or no transfusions [54]. Based on these data, the National Heart Lung and Blood Institute (NHLBI) expert guidelines recommend bringing the hemoglobin level to 10 g/dL for children and adults with SCD undergoing surgical procedures involving general anesthesia [29]. For individuals with higher baseline hemoglobin levels, such as those with HbSC and HbSβ^+ thalassemia, a modified (partial) or full (automated) red cell exchange transfusion prior to surgery requiring the use of general anesthesia may be favored over simple transfusion to prevent hyperviscosity-related complications [29].

Chronic transfusion therapy in pregnant women with SCD

Pregnant women with SCD are at increased risk of recurrent acute pain episodes, particularly during and beyond the second trimester. In a multicenter study, 72 pregnant women with SCD were randomized to either chronic transfusion therapy, with a goal hemoglobin of 10–11 g/dL and goal HbS level $\leq$35%, or transfusions as needed for obstetric and medical emergencies. The chronically transfused group of women experienced a reduction in acute pain events during pregnancy, but the study was not adequately powered to detect a significant difference in maternal or fetal complications [55]. A meta-analysis of this randomized study and 11 cohort studies comparing prophylactic or chronic transfusions during pregnancy to on demand transfusions showed a reduction in maternal mortality, vaso-occlusive pain episodes, pulmonary complications (including pulmonary embolism), pyelonephritis, perinatal mortality, neonatal death, and preterm birth with the prophylactic transfusion strategy. The odds of pre-eclampsia, intrauterine fetal demise, small-for-gestational-age infants, or low-birth-weight infants did not differ between both groups [6,56]. Guidelines from the United Kingdom recommend prophylactic transfusions in pregnant women with SCD with serious medical, obstetric, or fetal complications, for women with twin pregnancies, and for those with recurrent acute pain episodes during pregnancy [6,57,58]. In the United States, it is accepted, standard of care practice among SCD experts to initiate prophylactic transfusion during the second or third trimester of pregnancy for women who experience recurrent severe acute pain episodes.

Transfusion considerations for hematopoietic stem cell transplant in SCD

Allogeneic-matched sibling donor transplant is the only curative option for SCD with robust evidence from clinical trials. Early studies utilized myeloablative conditioning regimens with bone marrow stem cell grafts [59-61]. Current approaches are investigating less intense conditioning or nonmyeloablative regimens, using related or mismatched donors, thus allowing extension to patients with chronic organ dysfunction [67,75]. To mitigate against acute SCD-related post-transplant complications, based on expert consensus, patients receive an exchange blood transfusion before transplant to reduce HbS $<$35%, followed by simple transfusions to maintain hemoglobin at 9–10 g/dL until erythroid engraftment occurs [76]. Most individuals with severe SCD require episodic blood transfusions for management of acute and chronic disease complications, thus they are frequently alloimmunized to HLA and minor red cell antigens, increasing their risk of graft rejection or poor allograft function. Transfusion reactions, including acute and delayed hemolytic reactions, have been observed despite immunosuppressive regimens. Allogeneic stem cell transplants have been associated with a risk of prolonged reticulocytopenia and severe acute hemolytic anemia in nonmyeloablative regimens [77]. Presence of alloantibodies targeting donor HLA within the recipient have been associated with decreased graft survival for solid organ and HLA-mismatched hematopoietic stem cell transplants [78]. HLA alloantibodies can be induced through pregnancy or transfusions, even with leukocyte reduced red cell transfusions [79]. The use of antithymocyte globulin as part of the preparative regimen for this patient population has been associated with a decrease in the risk of graft rejection [80].

Approach to management of transfusion challenges in peri-transplant period

Role of the transfusion medicine service: We strongly recommend consultation with transfusion medicine prior to transplantation, with extended red cell phenotyping using serologic or molecular methods to match for minor red cell antigens and reduce the risk of alloimmunization. We also advise review of all clinically significant minor red cell antigen discrepancies between the donor and recipient that may affect selection of red cells for transfusion in the pre-engraftment period. In heavily alloimmunized patients, adequate time should be allotted to allow the blood bank to procure rare red cell units to support transfusion needs during the engraftment period, which is often at least 30 days.

Management of alloimmunization: Despite the use of myeloablative conditioning regimens, mixed donor chimerism, a mixture of donor and host hematopoietic stem cells within the bone marrow, persists in 10–20% of transplanted children with SCD [62,63], with an even higher proportion in adults receiving nonmyeloablative regimens [63]. Stable mixed chimerism with $\geq$25% donor myeloid cells and 100% donor erythroid cells, despite discontinuation of immunosuppression and abrogation of SCD-related symptoms, suggest immune tolerance of the allograft [63]; recipients should therefore be transfused according to the ABO type of the donor. Heavily alloimmunized individuals with SCD should be counseled on the risk of developing new auto- and alloantibodies to minor red cell antigens during the peritransplant period. In a single-center retrospective cohort study of 61 patients with SCD undergoing nonmyeloablative bone marrow transplantation with HLA-matched or haploidentical donors, 11 new alloantibodies and 2

Table 3a
Therapies to support alloimmunized individuals undergoing curative allogenic stem cell transplantation for severe sickle cell disease

Therapy	Mechanism of action	Notes	Reference(s)
Eculizumab	Monoclonal anti-CD5 antibody targeting the terminal complement cascade	Option to reduce intravascular hemolysis in individuals with delayed hemolytic transfusion reactions secondary to minor red cell antigen incompatibility	Dumas et al. Blood. 2016 Feb 25;127(8):1062-4. [1]
Hemoglobin-based oxygen carriers	Mainly used in Jehovah witness patients to reduce transfusion requirements while maintaining oxygenation of distal tissues	In the absence of high quality data, can consider the use of hemoglobin-based oxygen carriers for highly alloimmunized individuals with SCD for whom rare red blood cell units cannot be procured through the American Rare Donor Program or international equivalent procurement agency	Al. Biomolecules. 2017 Jan 4;7(1).[2]

new autoantibodies were detected in a total of 6 out of 61 patients (9.8%) after transplant [64]. However, larger prospective studies are warranted to determine the incidence of new auto- and alloantibodies in the post-transplant period for this population. Table 3a summarizes potential therapies to support alloimmunized individuals with SCD undergoing hematopoietic stem cell transplant for whom phenotypically matched red cell units may not be readily available.

Transfusion support peri-transplant: In order to minimize the risk of alloimmunization to minor red cell and HLA antigens prior to transplant, we agree with expert recommendations to transfuse leukoreduced, sickle negative red cells that are at least matched for Rh and Kell antigens, if extended phenotypic matching is not feasible due to time or resource constraints [29,65,66]. Cellular manipulation of the bone marrow graft prior to transplant in individuals with SCD has not been standardized and requires expert consultation with a stem cell transplant physician. Ex vivo T-cell depletion strategies to reduce the rates of graft rejection and graft versus host disease have been described in individuals with SCD undergoing haploidentical donor bone marrow transplant [67]. T-cell depletion strategies have been even more encouraging in children with thalassemia undergoing haploidentical bone marrow transplant [68], with no graft versus host disease, although the conditioning regimen was intense [69]. Approximately 25–50% of hematopoietic stem cell transplants involve ABO incompatible donors and recipients [70-72]. Bone marrow grafts are the preferred hematopoietic stem cell source for patients with SCD to minimize risk of graft versus dose disease, as there is no need for a graft versus tumor effect. However, bone marrow grafts contain a higher hematocrit with increased red cell content compared to other stem cell sources, which could increase the risk of an acute hemolytic episode, delayed red cell engraftment and pure red cell aplasia when major or bidirectional ABO mismatch is involved [72]. We recommend expert consultation with a stem cell transplant physician and the cellular processing laboratory to discuss the role of red cell depletion of the bone marrow graft in these specific clinical situations (Fig. 1).

Special transfusion considerations in SCD

Transfusion support in children with SCD

The typical red cell dosing recommended for the pediatric population is 10–15 mL/kg, whereas in adults and adolescents, 1–2 units of red cells are typically transfused in one setting, depending on the pre-transfusion hemoglobin level. The average response to transfusion is a rise in hemoglobin level by 1–2 g/dL, although this can be affected by the type of anticoagulant preservative solution used, as well as the rate of baseline hemolysis in the recipient. Multiple studies have demonstrated no benefit of fresher versus older blood in children, although there are concerns about extracellular potassium leakage in red cells that are stored for prolonged periods of time in infants receiving massive transfusions. A study of 290 children with anemia due to malaria or SCD showed no difference in survival, cerebral perfusion, electrolyte abnormalities, or lactate clearance for older red cells (stored for 25-35 days) when compared to fresher red cells (stored for $\leq$10 days) [73]. Nonetheless, when massive transfusions (>15-20 mL/kg of body weight) are administered to neonates, fresher red cells are preferred ($\leq$7-10 days of age) in order to avoid transfusing high levels of potassium and lactate.

In smaller children with low body weight and blood volume, the risk of hypovolemic and metabolic complications is increased with apheresis procedures [74]. For smaller children, the extracorporeal volume, defined as the minimum amount of blood volume needed to fill the circuit of an apheresis machine, can represent a significant percentage of their total blood volume, thereby increasing the risk of hemodynamic complications and worsening of anemia. Consensus guidelines recommend performing a priming with RBCs when the extracorporeal volume is at least 15% of the total blood volume, when the child weighs less than 20 kg, or when there are complications present such as severe anemia, cardiopulmonary disease or hemodynamic instability [75]. The option to input priming is already included in some commercially available apheresis systems [74].

Transfusion support for patients with SCD in low resource settings

Transfusion support in low-income countries has unique challenges [76], including inadequate blood supply [77,78], increased risk of transfusion transmitted infections [79-81], alloimmunization due to limited capacity for extended red cell phenotypic matching by molecular and serological methods [82-86], end organ damage from iron overload [87,88], inability to provide adequate blood components to support clinical needs and poor acceptance of chronic transfusions by patients due to sociocultural factors [89]. Table 3b summarizes challenges in transfusion practices in West Africa, where the majority of individuals with SCD reside.

The risk of organ damage from iron overload is higher in individuals SCD who are receiving chronic transfusions in low- and middle-income countries. Financial constraints arise from the cost of monitoring of iron overload by methods which are readily available in high resource settings (ferritin monitoring, liver biopsy, or liver magnetic resonance imaging T2*), and the cost of iron chelation itself [90]. The mean annual cost of chronic transfusions without chelation in Nigeria has been estimated at $3276.18. High cost and possibly socio-cultural fears related to blood transfusion may explain the poor acceptance of chronic transfusion programs by patients. In summary, because blood transfusion therapy is an integral component of the management of SCD, improved efforts and strategies to overcome these challenges and optimize blood transfusion practices are needed in low- and middle-income countries.

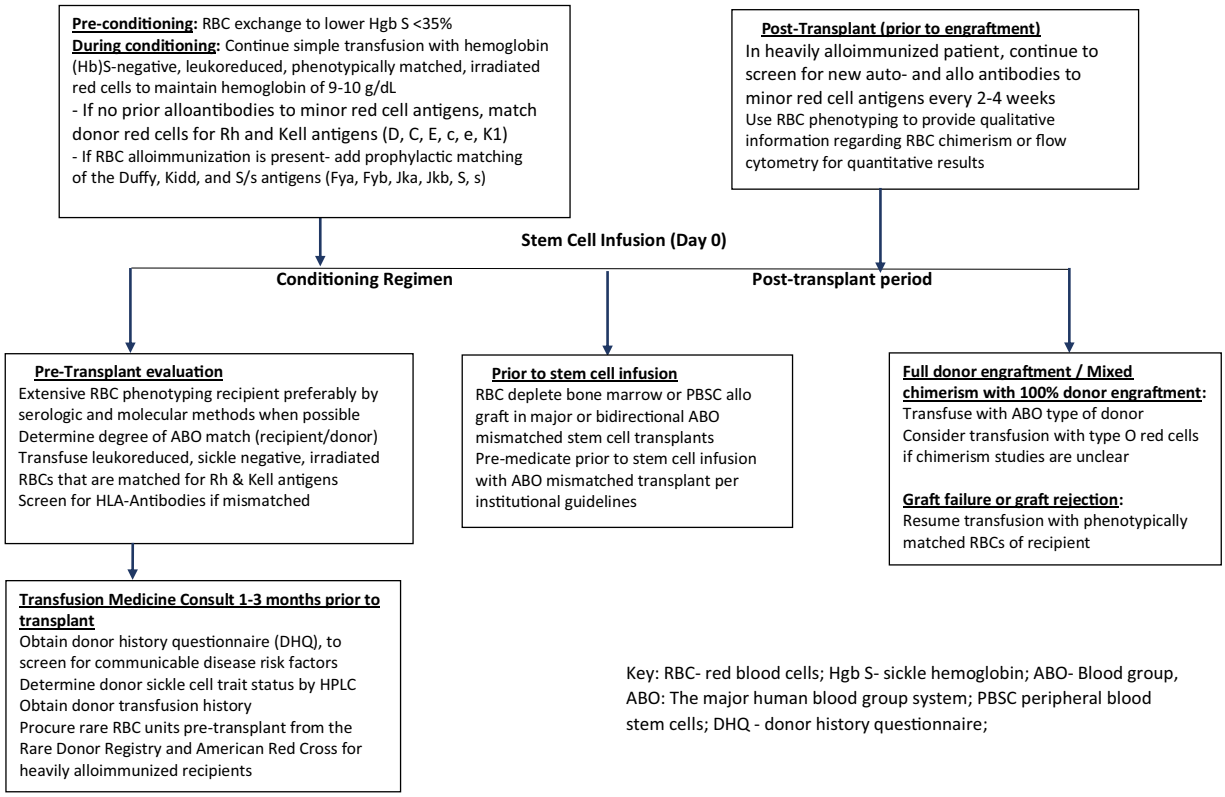

Fig. 1. Suggested approach for transfusion support in the peritransplant period in individuals with SCD undergoing allogeneic HSCT.

Table 3b
Challenges associated with transfusions for individual with SCD in West Africa

Challenges	Reference
Higher rates of acute on chronic anemia in West Africa due to infections such as malaria	Lund et al. Transfus Apher Sci. 2013;49(3):416-21.[3]
Reliance on replacement or paid donors with an antecedent increased risk of transfusion transmissible infections	Tagny et al. Transfusion. 2008;48(6):1256-61.[4] Jain et al. Asian J Transfus Sci. 2012;6(1):29-31.[5] Abdel et al. Blood Transfus. 2014;12(2):159-65.[6] Ajugwo et al. J Transm Dis Immun. 2017; 1 (2): 11.[7]
Low donation rate: The World Health Organization estimates that the donation rate in low-middle-income and low-income countries to be 7.8 and 4.6 donations per 1000 population, respectively, which is grossly inadequate to meet the current demand for blood products	origin.who.int/mediacentre/factsheets/fs279/en/WHOBsaaFsW.
Lack of resources for extended red cell antigen phenotyping and infectious disease screening beyond rapid screening tests, thereby increasing the risk of alloimmunization and transfusion transmitted infections, respectively	Diaku-Akinwumi et al. Int Health. 2016;8(5):330-5. [8]
Limited availability of apheresis machines to perform automated red cell exchange transfusions for acute and chronic complications of sickle cell disease	Diaku-Akinwumi et al. Int Health. 2016;8(5):330-5. [8]

Table 3c
Therapeutic limitations and risks associated with alloimmunization in individuals with sickle cell disease

Increased risk of delayed red cell engraftment and allograft rejection due to alloimmunization to minor red cell and HLA antigens in chronically transfused individuals
Delays in obtaining compatible red cell units
Hyperhemolysis
Delayed hemolytic transfusion reactions

Alloimmunization in SCD

Individuals with SCD have much higher rates of alloimmunization as a result of exposure to donor red cells compared to transfused individuals without SCD. Approximately 30% of individuals with SCD develop antibodies to minor red cell antigens during their lifetime, as compared to 2–5% of all transfused individuals [91]. Unfortunately, alloimmunization can lead to limitations in treatment, as summarized in Table 3c.

In the United States, most blood donors are Caucasian, while most individuals with SCD are of African descent, which leads to multiple red cell antigen discrepancies between the donor and recipient. In a single-center study of 203 chronically transfused patients with SCD, 20% (n = 40) were negative for a common group of antigens, with less than 1% of the Caucasian donor pool able to provide phenotypically matched, negative units [92]. Thus there is a need to increase recruitment of minority donors for chronically transfused individuals with SCD, as well as increase the use of molecular methods for prophylactic genotypic matching to maximize use of the minority donor pool.

Due to the high rates of alloimmunization in individuals with SCD, coupled with the need for repeated blood transfusions in many affected individuals, extended phenotypic matching beyond antigens of the Rh and Kell blood group systems is becoming increasingly more common as a strategy to prevent alloimmunization. Using either serologic or molecular methods, the minor red cell antigen expression profile of the recipient is determined, and

donor red cells are identified and transfused that have an identical minor red cell antigen expression profile. In the United States, clinical practice regarding antigen matching has been variable, as summarized in Table 3d.

The most common Rh phenotype in SCD patients is D + C − E − c + e+, which is found in less than 2% of Caucasians [93]. In order to provide red cell units that are negative for the C and E antigens, blood banks within the United States often provide red cells of the D − C − E − c + e+ phenotype, which are primarily obtained from Caucasian donors. However, this approach is problematic, as D negative red cell units comprise less than 15% of the blood bank inventory, and there is also the risk of exposing African-American recipients to immunogenic minor red cell antigens that are more frequent in Caucasians, such as Fya, Jkb, and S [93]. Even with the same exposure to transfusions, some individuals with SCD are more likely to alloimmunize; in immunologic terms, these individuals are referred to as "responders." Little is known of the genetic and biological determinants of this increased alloimmunization risk. A single-center retrospective cohort study of transfused individuals over a period of 15 years suggested that responder status is not dependent upon age, disease status, or number of alloantibodies already formed, and only weakly dependent on the number of prior transfusions [94].

Because standard serologic testing cannot distinguish variant Rh antigens, and single nucleotide polymorphism-based DNA assays can only test a limited number of RHD and RHCE variant alleles, whole exome sequencing has been explored as an alternative strategy to reduce Rh alloimmunization in individuals with SCD [95]. A study of 54 children and adolescents with sickle cell anemia, among whom 27 were alloimmunized to Rh antigens and 27 were age- and race-matched unalloimmunized controls, confirmed altered RH genotype as a risk factor for Rh alloimmunization in sickle cell anemia. Specifically, in the multicenter cohort, 52% of Rh immunized individuals vs 19% of those without Rh immunization expressed variant Rh alleles, and discrepancies in genotyping using whole exome sequencing and single nucleotide polymorphism arrays were detected in 19 samples [95]. At this time, whole exome sequencing is not standard practice for prophylactic matching of red cell units for individuals with SCD. The development of automated sequencing technology that allows longer read lengths and targeted next generation sequence panels for the RH loci may improve the accuracy, cost-benefit ratio, and feasibility of this approach for large academic medical centers. Future studies to determine biological, clinical, and genetic profiles of responders may help to direct novel genotyping resources to individuals with SCD with the greatest risk of alloimmunization.

Conclusions and future directions

Blood transfusion therapies for SCD are an integral and life-saving cornerstone of care for acute and chronic disease-related complications. As the life expectancy of adults with SCD continues to increase, rigorous multicenter studies will be necessary to determine the impact of transfusion therapy on overall survival and prevention of chronic vasculopathic disease complications outside the central nervous system. Currently, most randomized controlled trials demonstrating a benefit of chronic transfusion therapy for individuals with SCD have been conducted in children, with a focus on primary and secondary stroke prevention. Further, evidence-based strategies to measure the efficacy of chronic transfusion therapy for the prevention of stroke and other disease-related complications are lacking, raising the need for additional laboratory markers, in addition to HbS, to help establish clear goals of transfusion therapy.

Within the United States, there is currently tremendous practice-based variability for prophylactic red cell phenotyping,

Table 3d
Clinical practice regarding antigen matching for individuals with sickle cell disease in the United States

Study summary	Reference
Survey conducted by the American College of Pathologists: 743 out of 1182 labs reported that they did not routinely perform phenotypic matching for individuals with sickle cell disease Among the surveyed 330 labs that did perform phenotypic matching to prevent alloimmunization, 230 (85%) matched for the C, E and K1 antigens	Osby et al. Arch Pathol Lab Med. 2005;129(2):190-3. [9]
Survey of 50 academic medical centers: 73% reported that they routinely performed phenotyping matching	Afenyi-Annan et al. Transfusion. 2004;44(4):619-20. [10]
Protocols for phenotyping matching are highly variable: some institutions perform limited phenotypic matching for Rh and Kell blood group antigens only, with more extensive red cell phenotypic matching if one or more alloantibodies develop	Winkler et al. Immunohematology. 2012;28(1):24-6.[11] Vichinsky et al. Immunohematology. 2012;28(1):20-3. [12] Chou et al. Immunohematology. 2012;28(1):27-30. [13]
Some academic centers in the United States do not routinely perform phenotypic matching for individuals with sickle cell disease until they have become sensitized to minor red cell antigens and have developed detectable alloantibodies	Fasano et al. Immunohematology. 2012;28(1):13-6. [14] Karafin et al. Immunohematology. 2012;28(1):3-6. [15]

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both with regards to extent of phenotyping (ie, for C, E, and Kell antigens only, vs more extended matching for additional immunogenic minor red cell antigens) and with regards to the patient population of interest to target (ie, individuals with SCD who are already alloimmunized, vs all transfused individuals with SCD regardless of their alloimmunization status). Surveys show that the majority of American centers do not perform prophylactic red cell phenotyping. There is a need for a standardized, consensus-based approach to prevent alloimmunization in this population.

A critical aspect of advancing the management of this minority, socioeconomically disadvantaged population must also include the input of implementation scientists and health disparities researchers. Critical gaps in the accessibility of blood transfusion therapies, particularly automated red cell exchange transfusions, adversely affect children and adults with SCD in the United States, as well as those residing in low- and middle-income countries which have the world's largest population of affected individuals. Long-term strategies to improve the accessibility of automated red cell exchange transfusions will help to augment the quality of medical care for this population.

As an increasing number of individuals with SCD enroll in trials of hematopoietic stem cell transplantation or gene therapy, close collaboration between blood bank directors, hematologists, rare donor registries, and transfusion medicine physicians will be necessary to procure adequate numbers of compatible red cells to support transfusion requirements during the engraftment period. While advances in genotyping methods for the detection of RH variants has been described within the medical literature for the prevention of alloimmunization in SCD, automated, high throughput systems and targeted next generation sequence panels are necessary to increase the accuracy, cost, and feasibility of this approach for large academic centers. To date, the clinical, biological, and genetic factors that differentiate responders from nonresponders are poorly understood; individuals with SCD who have the greatest risk of alloimmunization would most benefit from prophylactic genotyping measures, which are more costly but also more accurate for detection of RH variants when compared to current serologic methods. Finally, efforts to increase the availability of genotyping methods to improve utilization of the African-American donor inventory, as well as focused strategies to increase recruitment of minority donors in high-income countries, will be necessary as adults with SCD continue to live longer and as our diagnostic algorithms for chronic SCD-related complications continue to improve.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.seminhematol.2020.07.007.

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