Review Article

Transfusion therapy in sickle cell disease

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Abstract: Sickle cell disease (SCD), the most common hemoglobinopathy worldwide after thalassemia, is characterized by a mutation in the β-globin gene that results in the production of hemoglobin S (HbS). HbS polymerizes under deoxygenated conditions, causing red blood cell (RBC) rigidity that leads to vaso-occlusion, hemolysis and endothelial damage. In addition to hydration, pain medication, and disease-modifying drug therapy, RBC transfusion is a mainstay of treatment. Simple or exchange (manual or automated) transfusions may be performed. RBC transfusions improve blood oxygen content, decrease HbS-containing RBCs, increase HbAA RBCs with normal oxygen affinity, and may suppress endogenous hematopoiesis. The goal of RBC transfusions is to decrease HbS levels to less than 30% and maintain the patient's hematocrit at less than 30%. The choice of performing a simple or exchange transfusion is partly dependent on the indication. Acute indications include acute stroke, acute chest syndrome (ACS), acute multisystem organ failure, intrahepatic cholestasis, hepatic/splenic sequestration, and priapism. Chronic indications include stroke prophylaxis, silent infarcts, recurrent ACS, recurrent painful episodes and complicated pregnancy. The frequency of RBC transfusions and quantity of RBC units transfused should be weighed against the risks of transfusion reactions. Aside from being at risk for the common transfusion reactions such as febrile nonhemolytic transfusion reactions and allergic reactions, patients with SCD are at an increased risk for alloimmunization, autoimmunization, iron overload and delayed hemolytic reactions with hyperhemolysis. This review discusses various aspects of transfusion therapy for SCD.

Keywords: Red blood cell transfusion; sickle cell disease (SCD); hemoglobin S

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Introduction

Sickle cell disease (SCD) is an inherited monogenic disease characterized by the β-globin gene mutation (1) hemoglobin S (HbS, β^6 glutamic acid-valine). SCD is an important hemoglobinopathy worldwide in terms of frequency and social impact, recently recognized as a global public health problem by the World Health Organization (2). In sub-Saharan Africa, up to one third of adults are carriers of the defective sickle cell gene, and 1% to 2% of babies are born with the disease (3). Globally, approximately 300,000 infants are born per year with SCD (4). The most common types of SCD are homozygous hemoglobin S (HbSS disease), hemoglobin SC disease, and sickle β thalassemia. HbSS disease and sickle β^0 thalassemia often are referred to as sickle cell anemia because they have similar severity (5).

SCD is a multisystem disorder with high morbidity and mortality. Hemoglobin polymerization, leading to erythrocyte rigidity and vaso-occlusion, is central to its pathophysiology, and chronic anemia, hemolysis, and vasculopathy are hallmarks of the disease (6). These physiologic derangements often lead to multiorgan damage throughout the lifespan. Acute, chronic, and acute-on-chronic complications contribute to end-organ damage and adversely affect life expectancy as well as quality of life (1).

Because polymerization of sickle hemoglobin (HbS) is the root cause of SCD complications, SCD therapies are focused on preventing HbS polymerization and reducing or suppressing the circulating amount of HbS (7). This review focuses on transfusion therapy as a supportive and preventive measure. Indications for transfusion, transfusion-related complications relatively specific to SCD, and methods for transfusion, i.e., simple and red blood cell (RBC) exchange are discussed.

Rationale and methods of transfusion in SCD

In patients without SCD, the typical purpose of red cell transfusion is to increase hemoglobin (Hb) to improve blood oxygen content according to the equation: $CaO_2 = (SaO_2 \times Hb \times 1.34) + 0.003(PaO_2)$ where CaO_2 is the arterial oxygen content, SaO2 is the arterial oxygen saturation and PaO_2 is the arterial oxygen tension. In SCD, however, there are two additional benefits of transfusion. One is lowering of the percentage of HbS-containing red cells with the capacity to undergo Hb polymerization under deoxygenated conditions; this is critical, because Hb polymerization is the root cause of all the downstream damage in SCD (8). For example, the resulting impaired rheology of deoxygenated red cells is sufficient to increase blood viscosity and slow blood flow velocity at arterial oxygen tension even without additional contributions from inflammation, adhesion, and endothelial and leukocyte activation (9,10), and there is improvement in sickle red cell rheology with transfusion (9,11). A second benefit is increasing the percentage of red cells with normal oxygen affinity, as HbSS red cells have lower oxygen affinity (12), probably due to high intracellular HbS concentration rather than high 2,3-DPG. This increases oxygen saturation at a given PaO_2, thus increasing blood oxygen content and decreasing the probability that HbS-containing red cells will reach the point of sickling with tissue oxygen extraction (13). A third theoretical benefit is that increasing Hb, given the longer life span of HbAA red cells, may decrease endogenous reticulocytosis and production of HbS-containing red cells (14,15), although studies have not demonstrated this to date (16,17). Transfusion can be administered through three methods, depending on clinical considerations and feasibility: simple transfusion (ST) [transfusion of allogeneic packed red blood cells (PRBC) without autologous red cell removal], manual red cell exchange (RCE) [autologous whole blood phlebotomy alternating with allogeneic PRBC and fluid infusion (18)], or automated RCE (removal of autologous RBC with allogeneic PRBC replacement using an apheresis device).

Simple transfusion

ST is the technically easiest method of transfusion, especially in acute clinical scenarios, due to the typical use of peripheral venous access and standard nursing. As is true in the general non-SCD population, ST is indicated with isolated symptomatic anemia, such as that resulting from parvovirus B19 aplastic crisis. It is important to point out, however, that SCD patients are anemic at baseline, with patients of SS and SB^0 genotype typically having chronic Hbs between 7–9 gm/dL (19-21). Furthermore, with vaso-occlusive episodes, SCD patients should receive hypotonic saline or D5W hydration to decrease MCHC and thus reduce HbS polymerization (22,23), hydration, however, will cause a lowering of the Hb without an actual decrease in blood oxygen content. Therefore, the standard restrictive transfusion thresholds (24,25) (typically 7–8 gm/dL) for transfusion established in randomized clinical trials may not be applicable to a SCD patient chronically tolerized to anemia. It is especially relevant to avoid unnecessary transfusion in uncomplicated vaso-occlusive episodes because the acute inflammatory state may increase the risk of red cell alloimmunization (26). However, even a clinically asymptomatic Hb <5 gm/dL is likely an indication for transfusion (in the absence of known hyperhemolysis), because acute anemia around 4 gm/dL or lower in SCD has been associated with acute silent cerebral ischemia and infarction (27). Others recommend ST with a fall in Hb ≥2 gm/dL below the baseline Hb, or in children, a Hb <6 gm/dL (28). Standard blood management practices such as minimizing phlebotomy for blood samples should be practiced.

ST has also been recommended by expert consensus for splenic sequestration (29,30). Limited case reports indicate potential safety of RCE for sequestration without hypotension (31), however, and RCE has the theoretical

advantage of potentially minimizing hyperviscosity issues that can occur when sequestered red cells re-enter the circulation. Even when RCE is preferable due to its ability to more rapidly lower HbS%, such as with acute stroke (32), transient ischemic attack (33), or rapidly progressive or severe acute chest syndrome (ACS) (34), ST may be indicated acutely as a temporizing measure until RCE can be performed. Finally, per the randomized controlled TAPS trial (35), ST to a Hb target of 10 gm/dL is indicated pre-operatively in SS or $S\beta^0$ patients with a baseline Hb <9 gm/dL undergoing surgeries requiring general or regional anesthesia; only 13 of 66 patients assessed in the trial had surgeries defined as low-risk, but one of those in the no-transfusion group had the serious adverse event of ACS after an umbilical hernia repair. Furthermore, a randomized trial (36) showed no significant differences in the peri-operative complications with ST versus RCE, including the most common serious complication of ACS, and the RCE group had a significantly higher rate of new red cell alloantibody development as well as delayed hemolytic transfusion reactions (DHTR).

ST, although requiring the least number of red cell units, has inevitable iron loading because no autologous red cells are removed (37,38). In a planned secondary analysis of transfusion data from the Silent Cerebral Infarct Multi-Center Clinical Trial, the median (interquartile range) ferritin level after 1 year of transfusions was 1,800 ng/mL (1,426–2,204 ng/mL) with ST, 1,530 ng/mL (1,205–1,805 ng/mL) with manual exchange, and 355 ng/mL (179–579 ng/mL) with automated exchange (P<0.001) (38).

In adults, ST of 1 red cell unit will typically increase the Hb in an average size adult by 1 gm/dL (and the Hct by 3%); children must be dosed by weight, and typically 10–15 mL/kg will increase the Hb by 2–3 gm/dL (39). In chronic ST, no more than about 3 units have been transfused per transfusion episode (37). Ideally, the volume of red cells needed to achieve the desired Hct should be precisely calculated as: $\frac{[(desired\ Hct - starting\ Hct) \times patient\ total\ blood\ volume]}{Hct\ of\ red\ cell\ unit}$ due to the risk of hyperviscosity or transfusion-associated circulatory overload (TACO). This is especially true in patients with pre-existing positive fluid balance or cardiovascular or renal disease, and rate of transfusion should be slow if clinically appropriate (40,41). The risk of hyperviscosity and TACO with ST typically precludes achievement of a HbS reduction to ≤30–50% in the acute setting; furthermore, increasing Hct to >30% without lowering the HbS ≤30% is not recommended, because the resulting increase in blood viscosity (42) may contribute to further vaso-occlusive complications, including posterior reversible encephalopathy syndrome and even death (43-45).

Exchange transfusion

Although automated and manual RCE require more red cell units than ST, their advantage is the ability to more rapidly achieve a low HbS level without an increase in hematocrit or total blood volume, if desired; iron loading (37,38,46), hyperviscosity, and TACO can thus be minimized. Compared to ST, RCE has an improved hematocrit:viscosity ratio, which is a mechanical estimate of oxygen delivery potential in the microcirculation (47). RCE has also been shown to result in an increase in arterial oxygen pressure, thus contributing to a further increase in Hb oxygen saturation (13,48); this is posited to be due to improvements in pulmonary microcirculation which may reduce ventilation-perfusion mismatching and intrapulmonary shunting. Importantly, the increased number of units used with chronic RCE has not been associated with increased red cell alloimmunization rates (49,50).

Both manual and automated methods require specialized expertise and supplies and may require central line placement; automated RCE of course requires the apheresis device. In manual RCE, whole blood removal alternates sequentially with replacement, whereas with automated RCE red cells selectively are removed and can be replaced concurrently. Therefore, manual RCE takes more time than automated RCE and has the additional risk of adverse events from volume shifts. Automated RCE also has the advantage of precise programming of the target HbS %, hematocrit, and overall fluid balance. It is recommended that a pre- and post-CBC and Hb fractionation be obtained to precisely tailor the programmed parameters (34). In patients whose extracorporeal volume with apheresis exceeds 10–15% of their total blood volume, an albumin prime is recommended.

Precise programming of the target fraction of cells remaining and increasing the target end Hct may be able to reduce red cell usage, as circumstances require (15). A modified automated RCE, in which RBC depletion by isovolemic hemodilution with saline or 5% albumin occurs prior to RCE, may also decrease red cell usage or increase the post-procedure Hct, associated with increased pre-procedure Hct (14,51). The increased pre-procedure Hct may be beneficial given that anemia is associated with silent brain infarcts in SCD (52). Isovolemic hemodilution should be avoided in clinical scenarios where induction of further

anemia may be detrimental, such as recent cerebral ischemic events; to reduce acute silent cerebral ischemic events (53), hemodilution should probably not decrease the hematocrit to less than 21% and/or more than 20% from baseline (34).

Regardless of method of transfusion, to minimize increased blood viscosity, the end hematocrit (Hct) goal of transfusion, for acute indications, is usually targeted no higher than 30% and the HbS target is <30% (54). Acute indications for RCE include acute stroke (32); rapidly progressive or severe ACS (34); multi-organ failure (55); fat embolism syndrome (56); acute sickle cell hepatic crisis, sickle cell intra-hepatic cholestasis, or acute hepatic sequestration (57,58); and pre-operatively in patients with SC and Sβ+ disease and Hb ≥10 gm/dL undergoing moderate-risk surgery (59) or patients undergoing very high risk surgery (34). For chronic indications, the end Hct is usually targeted no higher than 33-36% and the HbS target ranges between 30–50% (54), depending on the indication. Chronic indications for RCE or ST include prophylaxis against stroke (60,61), silent infarcts (62), recurrent ACS (62,63), recurrent painful episodes (62,63), and complicated pregnancy (34,54,64). After at least 1 year of chronic transfusion, hydroxyurea may be non-inferior to transfusion for primary stroke prophylaxis in patients with no Magnetic Resonance Angiography (MRA)-defined severe vasculopathy (65), but not for secondary stroke prophylaxis (66).

Indications for RBC transfusion

The indications for RBC transfusion in patients with SCD may be categorized as acute and chronic (67). Acute indications for RCE include acute stroke (32); rapidly progressive or severe ACS (34); multi-organ failure (55); fat embolism syndrome (56); acute sickle cell hepatic crisis, sickle cell intra-hepatic cholestasis, or acute hepatic sequestration (57,58); and pre-operatively in patients with SC and Sβ+ disease and Hb ≥10 gm/dL undergoing moderate-risk surgery (59) or patients undergoing very high risk surgery (34). Chronic indications for RCE include prophylaxis against stroke (60,61), silent infarcts (62), recurrent ACS (62,63), recurrent painful episodes (62,63), and complicated pregnancy (34,54,64). As noted above, after at least 1 year of chronic transfusion, hydroxyurea may be non-inferior to transfusion for primary stroke prophylaxis in patients with no MRA-defined severe vasculopathy (65), but not for secondary stroke prophylaxis (66).

In the absence of transfusion, stroke occurs in approximately 11% of patients with sickle cell anemia by the age of 20 (68,69). The Stroke Prevention Trial in Sickle Cell Anemia (STOP), where 130 children with SS or $S\beta^0$ were randomized to red cell transfusions to maintain HbS ≤30% or not, demonstrated that red cell transfusions significantly reduces the risk of a first stroke in children with SCD who have abnormal results on transcranial Doppler (TCD) ultrasonography (60). The mean interval between transfusions was 25±8 days. Only 1 child in the transfusion group had a stroke (cerebral infarction) as opposed to 11 children (10 cerebral infarctions, 1 intracerebral hematoma) in the standard of care group, which represents a 92% difference in the risk of stroke (P<0.001). Due to this compelling evidence, the trial was terminated early (60). The STOP trial led to the recommendations for TCD screening and prophylactic transfusion for children with abnormal velocities on ultrasonography (70).

Due to concerns of adverse effects with transfusing red cells indefinitely, the Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP II) trial was undertaken, where patients after ≥30 months of chronic transfusion were randomized to continue transfusion or not. The trial was halted after only 79 of the planned 100 patients were enrolled because almost half of the patients in the transfusion-halted group reached the primary composite end-point (2 strokes, 14 reversions to abnormal velocity on TCD) within 10 months after randomization, whereas none of the 38 children in the transfusion-continued group had an end-point event (P<0.001). Overall, this trial demonstrated that when red cell transfusions are discontinued in primary stroke prevention patients whose TCD velocities have normalized, there is a high rate of reversion to abnormal blood-flow velocities or stroke (61). In primary stroke prevention, the TWITCH trial showed that after 12 months of transfusion therapy, changing to hydroxyurea is non-inferior to transfusion in SCD children without severe vasculopathy (65), but in secondary stroke prevention, the SWITCH trial suggests that hydroxyurea is inferior to transfusion (66); there were no (0/66) strokes on transfusions/chelation but 10% (7/67) on hydroxyurea/phlebotomy when the trial was stopped for futility for lack of a difference in iron removal between the two arms.

ACS, characterized by fever, respiratory symptoms and a new pulmonary infiltrate, is the second most common cause of hospitalization and the leading cause of death in patients with SCD (71-73). Red cell transfusion early in the course of ACS has been found to hasten resolution (74), improve oxygenation (75,76), and reduce recurrence

(63,77). Several studies have implicated elevated levels of secretory phospholipase A2 (sPLA2) to be correlated with clinical severity of ACS (78-83). The feasibility study Preventing Acute Chest Syndrome with Transfusion Trial (PROACTIVE, ClinicalTrials.gov NCT00951808) was thus conducted to determine if elevation of serum levels of sPLA2 >100 ng/mL and fever could predict the development of ACS and whether ACS could be prevented by a single early transfusion of 7–13 mL/kg (79). Analysis of 203 subjects showed the sPLA2 threshold of >100 ng/mL to have a specificity of 82%, but sensitivity of only 41% and positive predictive value (PPV) of only 21%. sPLA2 ≥48 ng/mL provided the optimal trade-off between sensitivity (73%) and specificity (71%), but still only provided a PPV of 24%.

Patients with SCD frequently require surgery due to obstructive sleep apnea, adenotonsillar hypertrophy, cholelithiasis, splenic sequestration, and avascular necrosis. Perioperative complications related and not related to SCD are common. The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study was a multicenter, randomized clinical trial that assessed in pediatric and adult patients with HbSS or HbSβ^0 undergoing low- or medium-risk elective surgery whether perioperative complication rates would be altered by preoperative transfusion within 10 days of surgery to a target Hb of 10 gm/dL (35). Thirteen of 33 (39%) in the no-preoperative-transfusion group had clinically significant complications as opposed to 5/34 (15%) in the preoperative-transfusion group (P=0.023). Serious adverse events were observed in 10/33 (30%) subjects in the no-preoperative group and 1/34 (3%) subjects in the preoperative-transfusion group (95% CI: 1.2–12.2, P=0.027). Ten of the 11 serious adverse events were ACS (9 non-preoperative-transfusion group, 1 preoperative transfusion group). Hospital length of stay and readmission rates were similar between the two groups. Additionally, the study found that without preoperative transfusion, the need for perioperative transfusion was increased. Preoperative transfusion, therefore, is beneficial for patients undergoing low-risk and medium-risk surgeries (35). The type of RBC transfusion for pre-operative management depends on the patient's baseline Hb level (34). For patients with a Hb level less than 9 gm/dL, ST is recommended while for patients with a Hb level equal to greater than 9 gm/dL, RBC exchange transfusion to a HbS target <60% is recommended. The target Hb level in both cases should not exceed 11 gm/dL. For patients undergoing very high risk surgery such as neurosurgery or cardiac surgery, RBC exchange transfusion is recommended (34).

Pregnancy in women with SCD is associated with increased risks of sickle-related complications such as pain crises, pulmonary complications and infection; maternal and perinatal mortality, pregnancy-related complications; and fetal complications (84,85). Studies of the role of prophylactic red cell transfusions in pregnant women are limited (64,86-88). The only prospective randomized controlled study so far randomized 72 pregnant women with SCD to prophylactic transfusions versus on-demand transfusions for medical or obstetric emergencies (87). The incidence of painful crises was significantly reduced (P<0.01) and other SCD-related complications substantially reduced (P<0.07), but there was no significant difference in perinatal outcomes (87). However, a large meta-analysis did find a benefit for both maternal and neonatal outcomes (64). A study protocol has been designed to determine the feasibility and acceptability of a future phase 3 randomized controlled trial (89) to establish the clinical and cost effectiveness of serial prophylactic exchange blood transfusion in pregnant women with SCD (TAPS-2). Pregnant women will be randomized to receive red cell transfusion only when clinically indicated or automated RCE to maintain HbS-containing red cells <30% starting at or before 18 weeks of gestation until the end of pregnancy. In the meantime, current guidelines recommend considering prophylactic transfusion at regular intervals at the onset of pregnancy for women with: a history of severe SCD-related complications prior to current pregnancy; additional features of high-risk pregnancy (e.g., comorbidities or multiparity), or the development of SCD-related complications during the current pregnancy. A target Hb level of at least 7 gm/dL and HbS level of <50% is recommended (34).

Contraindications to transfusion in SCD include acute vaso-occlusive pain episodes and asymptomatic anemia (90). Vaso-occlusive pain episodes are primarily managed with supportive treatment, hypotonic fluid hydration, and pharmacologic drugs such as opioids but psychological, social and behavioral interventions may be incorporated for a more holistic approach (91). The treatment of asymptomatic anemia should be directed at the underlying cause (e.g., parvovirus B19 infection or renal insufficiency).

Adverse reactions to RBC transfusion

Red cell transfusions can lead to severe discomfort, morbidity or even mortality and increases healthcare costs (92). Patients with SCD may be at a greater risk for

transfusion reactions due to the higher number of red cell units transfused at one time. Febrile non-hemolytic transfusion reactions and allergic transfusion reactions are the most common types of transfusion reactions experienced by any patient receiving red cell transfusions. They have a prevalence of 1,000–3,000 per 100,000 units transfused and 112.2 per 100,000 units transfused, respectively (92). The less common but more serious transfusion reactions that could lead to significant morbidity and mortality such as acute hemolytic transfusion reactions (prevalence: 2.5–7.9/100,000 units transfused), DHTR (prevalence: 40/100,000 units transfused), transfusion related acute lung injury (prevalence: 0.4–1/100,000 units transfused), transfusion associated circulatory overload (prevalence: 10.9/100,000 units transfused), and septic transfusion reactions (prevalence: 0.03–3.3/100,000 units transfused) may also occur in the frequently transfused SCD patient population (92). This review will focus on three types of transfusion adverse events that are more specific for patients with SCD who are chronically transfused; namely, red cell antibody formation, iron overload and hyperhemolytic transfusion reaction.

RBC antibody formation

Alloantibody formation against RBC blood group antigens is a major complication for patients with SCD. Our understanding of the pathophysiological mechanisms that contribute to this phenomenon is limited. One factor that increases alloantibody induction in patients with SCD is their exposure to red cell antigens present in the blood donor population (mostly Caucasian) but lacking on their own red cells. Others factors are immune dysregulation in white blood cell subsets and their response to heme, platelets, RBCs and complement (93-96). The inflammatory status of the recipient at the time of RBC exposure may also influence whether a patient becomes alloimmunized or not; red cell transfusion in the setting of vaso-occlusive crisis, ACS, a viral illness, or other inflammatory disorder may increase the risk for alloimmunization (26,97,98).

In order to mitigate alloantibody formation, it is a common practice to match the RBC antigens for Rh D, C, and E, and K in accordance with the National Institutes of Health (NIH) Expert Panel, American Society of Hematology, and British Society for Haematology guidelines (30,34,43,99). The RBC alloimmunization rate is reported to be as high as 50% without any prophylactic matching but decreases significantly with prophylactic matching (100-102). With limited prophylactic matching (i.e., C, E, K), the RBC alloimmunization rate ranges from 5–24% (103) and with extended prophylactic matching that includes matching for Duffy, Kidd and S antigens, the RBC alloimmunization rate can be as low as 7% (104).

Even with transfusion of red cell units from African American donors matched for Rh D, C, and E, and K, however, 7 of 59 (12%) episodic and 55 of 123 (45%) chronically transfused patients with SCD were nevertheless Rh alloimmunized; 25 patients (40%) had greater than 1 Rh antibody (105). Rh alloimmunization was due to variant *RH* genes in either the transfused patients or their African-American donors, with both populations having 29% of RHD and 53% of RHCE alleles altered.

Patients with SCD may also develop autoantibodies. SCD disease-related inflammation and RBC membrane changes with neoantigen exposure may contribute to the predisposition for autoantibody formation. One retrospective study found that 29% (23/78) of pediatric patients developed clinically significant alloantibodies and 8% (6/78) also developed autoantibodies. Four of these 6 patients (66%) had previously identified IgG alloantibodies (106). Autoantibodies may cause clinically significant hemolysis and complicate the immunohematology workup as well as subsequent pRBC crossmatching.

Iron overload

Repeated STs, as is required for patients with SCD, may lead to iron overload. Each pRBC unit contains approximately 200–250 mg of iron, about the amount normally absorbed in one year (107,108). Iron is retained and recycled by the reticuloendothelial system in the body and there is no physiologic regulatory mechanism for excreting excess iron. Senescent RBCs are phagocytized by macrophages (34) in the liver and spleen, where iron is scavenged into endosomes and delivered to the vascular space via ferroportin (107,109). Once in the plasma, the iron is rapidly bound by serum transferrin and transported to the bone marrow. Excess transferrin-bound iron is taken up by the liver, which is where iron is predominantly stored in the body (107). When transferrin becomes completely saturated, non-transferrin bound iron may be deposited in the liver, heart, pancreas, endocrine glands, and joints (107,110). Studies have shown that iron may be transported by zinc (111) or calcium (112) transporters as well.

Iron overload may occur after approximately 10–20 units of pRBC are transfused. In general, a 15 mL/kg transfusion

will raise hepatic iron, normally less than 1.5 mg/g dry weight (113), by approximately 1 mg/mL dry weight (114). Among 12 pediatric patients with an average of 15.4 transfusions over 21 months, the mean liver iron concentration (LIC) was 9.4 mg/g dry weight without chelation therapy (115), a level at which one starts to see portal fibrosis. Therefore, patients with a history of at least 10 transfusions and a serum ferritin >1,000 mcg/L should undergo magnetic resonance imaging (MRI) of the liver to detect iron overload. MRI is the gold standard for monitoring iron levels in various organs of the body due to its accuracy, reproducibility and tolerability by patients (107); the same method (R2, T2* or R2*) should be used over time. Given that cardiac iron loading is uncommon in SCD, cardiac MRI should be considered only with high iron burden (LIC >15 mg/g) for 2 years or more, evidence of end organ damage due to transfusional iron overload, or evidence of cardiac dysfunction (34).

Iron chelation, by which the three FDA-approved agents differ by route of administration, half-life, and toxicities, should be started once the LIC is >3 mg/g, and definitely once the LIC is >7 mg/g (113). Over 1 year, a similar dose-dependent decrease in liver iron content was observed with oral deferasirox (–3.0±6.2 mg Fe/g dry weight) and intravenous/subcutaneous deferoxamine (–2.8±10.4 mg Fe/g dry weight) (116). Deferiprone may be the most effective agent with cardiac iron overload (113).

Hyperhemolytic transfusion reaction

A small percentage of transfused patients with SCD (1–4%) experience a hyperhemolytic transfusion reaction (HHTR), defined by a rapid Hb decline to below the pre-transfusion level accompanied by a rapid decline of post-transfusion HbA level about 7–10 days after RBC transfusion (34,117,118). Autologous as well as transfused red cells are hemolyzed in a phenomenon called "bystander hemolysis" (119,120). Most patients also have a negative antibody screen and direct antiglobulin test, signifying the absence of any detectable antibodies (118), although occasionally, patients may exhibit a new alloantibody or autoantibody (121). Possible mechanisms of bystander hemolysis include increased red cell exposure of phosphatidylserine (119), antibodies to antigens other than red cell antigens (120), macrophage activation by the inflammatory milieu (117,122-124), and alternative complement activation by heme (125). Such mechanisms are not mutually exclusive—for example, exposure of phosphatidylserine on the outer membrane of HbS-containing RBCs increases macrophage adherence compared to HbA-containing RBCs (126).

Continued RBC transfusion may lead to death in patients with HHTR, as it may further exacerbate hemolysis (117,127). The type of treatment to administer depends on the severity of anemia and briskness of hemolysis. Supportive care includes erythropoietin with or without IV iron, oxygen as needed, and limiting activity to minimize oxygen consumption. Mild HHTR may be treated with steroids, while more severe hemolysis should also be treated with intravenous immunoglobulin (IVIG) (117,128). Second-line treatments include eculizumab, a monoclonal antibody that inhibits the complement pathway by blocking cleavage of C5, in order to decrease hemolysis; and/or rituximab, an anti-CD20 monoclonal antibody, in order to prevent red cell alloantibody production if further transfusion is necessary (129-132). Tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, was used successfully in an HHTR case with hyperferritinemia under the premise of activated macrophage inhibition (133).

Conclusions

Despite advances in therapeutic options for patients with SCD, transfusion therapy remains a mainstay. There are immediate benefits to transfusion, such as lowering of the percentage of HbS-containing red cells with the capacity to undergo Hb polymerization under deoxygenated conditions. In addition, transfusion increases the percentage of RBC with normal oxygen affinity, thus increasing oxygen saturation and blood oxygen content and decreasing the probability that HbS-containing red cells will reach the point of sickling. Transfusion of RBCs can be delivered via three methods including ST, manual RCE, or automated RCE. Each of these methods carry advantages and disadvantages as described above. The choice of delivery method for a specific patient will depend on clinical considerations and feasibility.

Regardless of method of transfusion, the indications for RBC transfusion in patients with SCD may be categorized as acute and chronic. As general rule of thumb, the end hematocrit (Hct) goal of transfusion, for acute indications, is usually targeted no higher than 30% and the HbS target is <30%; Similarly, for chronic indications, the end Hct is usually targeted no higher than 33–36% and the HbS target ranges between 30–50%, depending on the indication. There are also contraindications to transfusion in SCD, such as acute vaso-occlusive pain episodes and asymptomatic

anemia. Last but not least, one has to consider the risks associated with transfusion therapy: transfusion reactions, increased risk for alloantibody and autoantibody formation, development of iron overload, and hyperhemolysis.

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