Chapter 6: Blood Transfusion in the Management of Sickle Cell Disease

Introduction

Donor erythrocyte (red blood cell, RBC) transfusion was the first therapy used in SCD that targets the pathophysiology of SCD, even though transfusion was used before the basic pathophysiology of SCD was understood.[388] Donor erythrocytes contain normal hemoglobin (HbA), and transfusion of these donor RBCs into people with SCD reduces the percentage of circulating erythrocytes with abnormal hemoglobin (HbS). Although donor erythrocyte transfusion can ameliorate and even prevent SCD manifestations in select circumstances, transfusion of donor erythrocytes is not universally beneficial in SCD. Many of the recognized hazards of transfusion, such as the risk of alloimmunization, are amplified in SCD[389]; therefore, decisions to utilize transfusion therapy in SCD must be based on risk-benefit assessments. The goal of this chapter is to present evidence-based recommendations that summarize the indications, risks, and benefits of erythrocyte transfusion therapy in SCD.

Background

Sickled erythrocytes possess many unfavorable physiologic properties and induce vascular changes that promote vaso-occlusion. Sickled erythrocytes increase blood viscosity through intrinsic properties of the sickled cells as well as abnormal interactions of these cells with leukocytes, platelets, vascular endothelium, and clotting factors. Transfusion of donor erythrocytes is used in some situations to mitigate these effects with favorable results. Over the last three decades, the number of evidence-based indications for erythrocyte transfusion in SCD has been increasing. Ongoing studies of transfusion in SCD may provide evidence for additional indications for transfusion. As erythrocyte transfusion becomes more commonplace in the care of people with SCD, it is important to understand the evidence that supports its use in specific clinical situations.

To minimize adverse effects of transfusion, the selection and infusion of erythrocyte units should follow standard blood banking and transfusion practices. Many institutions provide all people with SCD with erythrocyte units that are sickle negative and leukocyte reduced; to prevent alloimmunization, many institutions also routinely provide units matched for minor Rh and Kell antigens.[390-392] The clinical benefits of transfusing sickle-negative RBCs in SCD (as compared to sickle trait RBCs) have not been specifically studied. Transfusing sickle-negative erythrocytes assists with accurate tracking of percent sickled hemoglobin when specific HbS targets are used and avoids the possibility of the transfused erythrocytes becoming sickled, which has been described in extreme circumstances.[393,394] A specific request of the blood bank may be required to obtain sickle-negative erythrocytes.

Sickle cell anemia (SCA) refers to the clinically similar disorders HbSS or HbSβ^0-thalassemia. Sickle cell disease (SCD) refers to all disease genotypes, including SCA and compound heterozygous disorders, such as HbSC, HbSD, and HbSβ+-thalassemia. The carrier state for hemoglobin S (HbAS or sickle cell trait) is not a form of SCD.

Approximately 70 percent of RBC units currently collected in the United States are leukoreduced before storage,[395] and, by extension most RBC units given to people with SCD are leukoreduced. The benefits of transfusing leukoreduced erythrocytes in SCD have not been studied specifically, although previously documented benefits of leukoreduction in other populations include lower incidences of febrile nonhemolytic transfusion reactions,[396] cytomegalovirus (CMV) transmission,[397] and Human Leukocyte Antigen (HLA) alloimmunization.[398] The benefits of using leukocyte-reduced erythrocytes are expected to be applicable to individuals with SCD who require transfusion.

Donor erythrocytes may be administered as a simple transfusion or as an exchange transfusion. Simple transfusion is the infusion of donor erythrocytes without removal of recipient blood, whereas exchange transfusion involves removal of recipient blood before and/or during donor erythrocyte infusion. Three benefits of exchange transfusion, related primarily to the removal of recipient sickle erythrocytes, include (1) increasing the percent of normal (donor) hemoglobin (HbA)-containing erythrocytes remaining after transfusion; (2) permitting transfusion of increased volumes of donor blood without increasing the hematocrit to levels that excessively increase blood viscosity; and (3) reducing the net transfused volume, which reduces iron overload. However, potential risks of exchange transfusion include (1) increased donor unit exposure and subsequent alloimmunization; (2) higher costs; (3) the need for specialized equipment; and (4) the frequent need for permanent venous access. Exchange transfusion can be accomplished by manual or automated (erythrocytapheresis) methods. The decision regarding the type of transfusion technique to employ is multifactorial and is guided by patient acuity, institutional expertise, and compatible blood supply.

Erythrocyte transfusion in SCD can be further classified as episodic or chronic. Episodic transfusion is used either acutely in response to a complication of SCD or prophylactically in preparation for anesthesia or surgery. Chronic transfusion is used when sustained, low levels of HbS are needed for primary or secondary prophylaxis for SCD complications, most commonly stroke in children. Chronic transfusion programs may use different blood matching and monitoring strategies, although the themes of avoiding transfusion reactions, minimizing alloimmunization, maintaining low HbS levels, and tracking and treating transfusional iron overload are common among all programs.[399]

Transfusions can be lifesaving and protect organs from ongoing damage from sickled erythrocytes in the appropriate setting but also can cause serious and occasionally life-threatening complications. Judicious application of erythrocyte transfusion therapy in SCD requires an understanding of the evidence for erythrocyte transfusion in specific clinical situations and an understanding of the additional risks of transfusion in people with SCD.

There are many potential indications for transfusion in the patient with SCD. This chapter discusses only the most common indications, including prophylactic perioperative transfusion; transfusion in the setting of acute occurrences such as stroke, multisystem organ failure, and acute chest syndrome (ACS); and transfusion in the setting of chronic occurrences such as primary and secondary prevention of stroke in children. Common transfusion side effects, including alloimmunization, autoimmunization, iron overload, hyperviscosity, and hemolysis, are also discussed.

Methodology

Complete information about the methodology for these guidelines can be found in the "Introduction and Methodology" chapter (pages 1–9). The following information, specific to this chapter, supplements the standard methodology that was conducted for all clinical chapters of these guidelines.

A comprehensive study of several databases was conducted, and all human studies in English published from 1970 to July 2010 that addressed each PICOS question were identified. A total of 300 studies were included.[j] In some cases in this chapter, a literature search was not conducted or the search yielded no evidence (e.g., management of hyperviscosity), so the expert panel relied on their cumulative expertise and knowledge to make recommendations; these recommendations are labeled "Consensus–Panel Expertise." The key questions for this chapter can be found immediately before the Summary of the Evidence sections for the individual topics.

Detailed information on the evaluated studies as well as the observational and case studies/series referenced can be found in the Transfusion in Sickle Cell Disease evidence table available at http://www.nhlbi.nih.gov/guidelines/scd/index.htm.

Indications for Transfusion

Prophylactic Perioperative Transfusion

Background

Transfusions are commonly used in the perioperative period to prevent the development of vaso-occlusive crises (VOCs), stroke, or ACS after surgery. Surgical procedures are associated with significant morbidity for individuals with SCD. In the Cooperative Study of Sickle Cell Disease (CSSCD), sickle-related complications (e.g., VOC, ACS, and stroke) occurred in 0–18.6 percent of patients with SCA (depending on the surgical procedure) and non-sickle cell-related complications (defined as fever, infection, bleeding, thrombosis, embolism, and death) occurred in 5.7 to 26.2 percent of patients. There were 12 deaths in 1,079 surgical cases.[400]

The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study was published in 2013 and thus was not included in the evidence review. However, the expert panel did want to acknowledge this important study. TAPS was a multicenter trial in Europe and Canada[401] that randomized individuals with SCA to either no preoperative transfusion or preoperative transfusion. The study enrolled patients undergoing low-risk (e.g., adenoidectomy, inguinal hernia repair) and medium-risk (e.g., cholecystectomy, joint replacement) procedures. The goal of transfusion was to raise the hemoglobin to 10.0 g/dL. In patients with preoperative hemoglobin levels of 9.0 g/dL or higher, a partial exchange transfusion was done. The study was closed early due to significantly more complications in the medium-risk, no preoperative transfusion arm than in the medium-risk transfusion arm (10/33 vs. 1/34). The unadjusted odds ratio of clinically important complications was 3.8. As the study was closed early, the estimate observed may be overestimated. There were too few patients enrolled in the low-risk procedure arms to draw any conclusions.

Key Question

KQ25. In patients with SCD undergoing surgical procedures, does a particular perioperative transfusion approach (simple or exchange transfusion to achieve a predetermined hemoglobin level or percentage of HbS) reduce perioperative mortality and complications?

[j] An updated search was performed to span the time from June 1, 2010 through July 11, 2014. One additional RCT was identified, for a total of 300 studies, and a supplemental table reflecting this addition was added to the evidence table document.

Summary of the Evidence

One RCT, four observational studies, and six case series evaluated perioperative transfusion outcomes in SCD. Overall, the quality of evidence was low due to severe imprecision (small number of events) and lack of controlled comparisons; therefore, the results are inconclusive.

A single randomized trial has been done examining the use of transfusion in the perioperative period.[402] This study compared the use of simple transfusion with a hemoglobin (Hb) goal of 10 g/dL preoperatively to the use of exchange transfusion to bring the HbS ≤30 percent. No statistically significant reduction in the incidence of perioperative complications was seen between the two arms of the study, although complication rates in both arms were high (31 percent in the exchange group and 35 percent in the simple transfusion group), and 10 percent of patients in both arms developed ACS.[402]

The four observational studies and six case series reported on various outcomes of transfusion in the perioperative period. In 717 patients with SCA undergoing surgical procedures in the CSSCD, the combined incidence of all sickle cell-related complications postoperatively was significantly lower in those who had preoperative transfusion compared to those who did not have transfusion.[400] Similar results were demonstrated in individuals with sickle hemoglobin C (HbSC) disease.[400]

Al-Samak et al.[403] described 46 patients who underwent simple transfusion, exchange transfusion, and no transfusion. The incidence of sickle cell crisis and ACS was similar in all three groups. Wali et al.[404] studied 14 patients and reported similar perioperative outcomes of conservative versus aggressive transfusion (Hb >10 g/dL and HbS <30 percent). The remaining seven studies were uncontrolled case series and did not provide additional conclusions.

Recommendations

1. In adults and children with SCA, transfuse RBCs to bring the hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia.
   (*Strong Recommendation, Moderate-Quality Evidence*)
2. In patients with HbSS disease who require surgery and who already have a hemoglobin level higher than 8.5 g/dL without transfusion, are on chronic hydroxyurea therapy, or who require high-risk surgery (e.g., neurosurgery, prolonged anesthesia, cardiac bypass), consult a sickle cell expert for guidance as to the appropriate transfusion method.
   (*Strong Recommendation, Low-Quality Evidence*)
3. In adults and children with HbSC or HbSβ^+-thalassemia, consult a sickle cell expert to determine if full or partial exchange transfusion is indicated before a surgical procedure involving general anesthesia.
   (Moderate Recommendation, Low-Quality Evidence)

Recommendations for Acute and Chronic Transfusion Therapy

Exhibits 14–19 summarize the expert panel's recommendations for transfusion therapy in acute and chronic complications. A more detailed discussion of the indications for transfusion and the evidence to support these recommendations for each disorder can be found in the chapters on health maintenance, acute complications, or chronic complications. Exhibits 14–19 are designated as either graded or consensus recommendations.

Exhibit 14. Acute Complications—Graded Recommendations To Transfuse

Indication	How To Transfuse	Quality of Evidence	Strength of Recommendation
Symptomatic acute chest syndrome (ACS) combined with a decreased Hb of 1 g/dL below baseline	Simple transfusion	Low	Weak
Symptomatic severe ACS (as defined by an oxygen saturation less than 90% despite supplemental oxygen)	Exchange transfusion	Low	Strong
Acute splenic sequestration plus severe anemia	Simple transfusion	Low	Strong
Stroke	Simple or exchange transfusion	Low	Moderate

Exhibit 15. Acute Complications—Consensus Recommendations To Transfuse

Indication	How To Transfuse
Hepatic sequestration	Exchange or simple transfusion
Intrahepatic cholestasis	Exchange or simple transfusion
Multisystem organ failure (MSOF)	Exchange or simple transfusion
Aplastic crisis	Simple transfusion
Symptomatic anemia (see page 43 in the "Managing Acute Complications of Sickle Cell Disease" chapter)	Simple transfusion

Exhibit 16. Acute Complications—Graded Recommendations When Transfusion Is Not Indicated

Indication	Quality of Evidence	Strength of Recommendation
Uncomplicated painful crisis	Low	Moderate
Priapism	Low	Moderate

Exhibit 17. Acute Complications—Consensus Recommendations When Transfusion Is Not Indicated

Indication
▪ Asymptomatic anemia ▪ Acute kidney injury, unless multisystem organ failure (MSOF)

Exhibit 18. Chronic Complications—Graded Recommendations for When To Initiate a Chronic Transfusion Program

Indication	How To Transfuse	Quality of Evidence	Strength of Recommendation
Child with transcranial Doppler (TCD) reading* >200 cm/sec	Exchange or simple transfusion	High	Strong
Adults and children with previous clinically overt stroke	Exchange or simple transfusion	Low	Moderate

* TCD reading is the time averaged mean maximal cerebral blood flow velocity. See section about Screening for Risk of Stroke Using Neuroimaging in the "Health Maintenance for People With Sickle Cell Disease" chapter.

Exhibit 19. Chronic Complications—Graded Recommendations for When Transfusion is Not Indicated

Indication	Quality of Evidence	Strength of Recommendation
Recurrent splenic sequestration	Low	Weak

Appropriate Management/Monitoring

The administration of RBC transfusions is common in both children and adults with SCD. In this area, the expert panel reviewed literature to answer questions about phenotype matching, the goals of transfusion therapy, and appropriate monitoring in chronically transfused individuals. Studies have tried to answer whether giving phenotypically matched red cells decreases the risk of alloimmunization in people with SCD. In addition, questions have arisen about the appropriate transfusion goals for patients undergoing transfusion both acutely and chronically. The expert panel was able to make recommendations for goals of chronic transfusion therapy in children, but evidence was insufficient to propose a goal HbS concentration for chronically transfused adults, as it may vary by indication.

This section concludes with a consensus-based protocol on appropriate monitoring of patients who receive chronic transfusions. The protocol contains several technical remarks and recommendations needed to implement chronic transfusion therapy safely and effectively. The protocol should be considered as guidance and modified to fit an individual patient's clinical situation.

Key Question

KQ26. In patients with SCA who require RBC transfusion, what are the most effective transfusion protocols that reduce transfusion complications (including a transfusion goal, phenotype-matching monitoring approaches, procedures, or strategies)?

Summary of the Evidence

Phenotype Matching

Four RCTs, 63 longitudinal and cross-sectional studies, and 46 case reports were identified that demonstrated alloimmunization. In the four RCTs (with >1,100 patients), alloimmunization/autoimmunization development rates ranged between 3 percent and 29 percent.[98,402,405,406] In the other 63 studies (involving >6,000 patients), alloimmunization rates ranged between 6 percent and 85 percent, and autoimmunization rates ranged between 4 percent and 10 percent. Overall, minimal evidence is available to support a particular method to reduce or prevent side effects from RBC transfusion.[407]

The systematic review did not identify comparative effectiveness studies that explored different cross-matching approaches. Two studies (one RCT and one observational study involving 159 patients) that implemented stricter matching criteria had more favorable results (alloimmunization rates <7 percent)[408,409] The definition of a "strict cross match" varied among studies, and often included matching for ABO and a number of other RBC antigens, including DCcEe and Kell, and occasionally Kidd and Duffy.[409] In the published studies, to prevent alloimmunization or to transfuse patients who were already alloimmunized, investigators most commonly opted to use strictly phenotype-matched RBC units.

Transfusion Goals

The systematic review did not identify evidence supporting the effectiveness of a specific HbS percentage cutoff for transfusion (i.e., there are no comparative studies in which different HbS targets were evaluated). In the transfusion protocols used in the included randomized trials of patients treated with chronic transfusion, two (both in children) used a cutoff of ≤30 percent (STOP 1 and 2),[96,98] while the remaining trial, which studied the use of chronic transfusion in pregnancy, used a cutoff of hemoglobin between 10 g/dL and 11 g/dL[405] and a HbS cutoff of ≤35 percent. The ≤30 percent cutoff was used in roughly 75 percent of the observational studies (a total of 2,648 adults and 4,523 children). However, it is unclear how the use of these cutoffs correlates with outcomes. In the two multicenter stroke prevention trials, this cutoff was beneficial in reducing the risk of stroke (compared to no transfusion). These data may guide the practice of transfusion in SCD and suggest a particular transfusion goal; however, the evidence is indirect and of low quality.

No studies evaluated the effectiveness of different monitoring strategies.

Recommendations

1. RBC units that are to be transfused to individuals with SCD should include matching for C, E, and K antigens. (***Moderate Recommendation, Low-Quality Evidence***)
2. In patients with SCA, who are not chronically transfused and who are therefore at risk for hyperviscosity due to high percentages of circulating HbS-containing erythrocytes, avoid transfusing to a target hemoglobin above 10 g/dL. (***Moderate Recommendation, Low-Quality Evidence***)
3. In chronically transfused children with SCA, the goal of transfusion should be to maintain a HbS level of below 30 percent immediately prior to the next transfusion. (***Moderate Recommendation, Moderate-Quality Evidence***)
4. The expert panel recommends that clinicians prescribing chronic transfusion therapy follow an established monitoring protocol. (***Moderate Recommendation, Low-Quality Evidence***)

Although the literature does not offer evidence comparing different implementation protocols for chronic transfusion therapy, the expert panel was concerned about inadequate monitoring if a protocol is not used. Hence, taking into account the evidence supporting the use of routine monitoring, the expert panel issued a recommendation for adopting a standardized protocol to maximize benefits and safety. A suggested protocol was developed by the expert panel based on (1) protocols used in the published clinical trials and observational studies, (2) indirect evidence derived from basic science, and (3) a consensus process. The protocol contains several technical remarks and recommendations needed to implement chronic transfusion therapy safely and effectively, but the protocol should be considered as guidance and modified to fit an individual patient's clinical situation.

Consensus Protocol for Monitoring Individuals on Chronic Transfusion Therapy

The following is a consensus protocol for the initiation and monitoring of patients on chronic transfusion therapy. It is understood that the recommended testing schedule may not be available to patients everywhere; therefore, this protocol should serve only as a helpful guide for transfusion management.

At Initiation

- Obtain patient treatment history to include locations where prior transfusions were received and any adverse effects.
- Notify the blood bank that the patient being initiated on chronic transfusion therapy has SCD. Ask the blood bank to contact hospitals where the patient reported receiving previous transfusion therapy to obtain transfusion information.
- Obtain a RBC phenotype, type and screen, quantitative measurement of percent HbA and percent HbS, complete blood count (CBC), and reticulocyte count.
- Inform the patient if he or she is alloimmunized, so that this information can be communicated as part of the patient's self-reported medical history.

Suggested Evaluation Before Each Transfusion

- CBC and reticulocyte count—This procedure is done to help guide the frequency and volume of transfusions. It is expected that, with effective chronic transfusion therapy, the patient's bone marrow will be suppressed and the reticulocyte count should decrease, but the value may rise by the time of the next transfusion.
- Quantitative measurement of percent HbA and percent HbS—This procedure is done to confirm the success of chronic transfusion therapy with achieving the target percent of HbS.
- Type and screen—This is done to assess whether the patient has developed any new RBC antibodies from the prior transfusion.

Suggested Periodic Evaluations

- Liver function tests annually or semiannually—These tests are done to follow liver function in individuals with iron overload.
- Serum ferritin (SF) quarterly—This test is done to follow iron stores in individuals with iron overload; it can be helpful in evaluating compliance with chelation.
- Screening for hepatitis C, hepatitis B, and HIV annually.
- Evaluation for iron overload every 1–2 years by validated liver iron quantification methods such as liver biopsy, MRI R2 or MRI T2* or R2 techniques.

Complications of Transfusions

Overview

Although RBC transfusions can help ameliorate many of the acute and chronic complications of SCD—and, at times, can be life-saving—their administration is associated with a wide variety of complications. Some transfusion-associated events are relatively mild, while others can be severe or even fatal. Health care providers should become familiar with the range of transfusion complications and learn their signs and symptoms as well as appropriate diagnostic testing, prevention strategies, and therapeutic interventions when warranted.

This section discusses alloimmunization, autoimmunization, iron overload, hemolysis, and hyperviscosity—the most commonly occurring side effects of transfusion. After a description of the side effects and a summary of the evidence, this section concludes by identifying some areas in which additional research is needed.

Alloimmunization and Autoimmunization

Background

Human erythrocytes express a large number of surface proteins, glycoproteins, polysaccharides, and glycolipids that are potentially immunogenic. Following an erythrocyte transfusion, if the donor erythrocytes have a different antigenic profile from those of the recipient's own erythrocytes, an immunological response by the recipient against the "foreign" antigens can result in a process known as alloimmunization. Polysaccharide antigens generally elicit only immunoglobulin M (IgM) responses, but other erythrocyte antigens elicit an immune response that begins with production of polyclonal IgM alloantibodies within 3–7 days of antigenic stimulation and then evolves to polyclonal IgG alloantibodies over several weeks.

Immunoglobulin G (IgG) alloantibodies persist for many years, although their titer may wane to low or undetectable levels. Almost all IgM alloantibodies, and some IgG alloantibodies, can bind to the transfused erythrocytes and fix complement, a set of serum proteins that bind to the erythrocyte and cause direct hemolysis. The result of alloimmunization is usually destruction of transfused erythrocytes that express the antigen, but the pathophysiology of red blood cell destruction and immune-mediated clearance is complex and depends upon several features including the antibody isotype, titer, and ability to fix complement. Occasionally, the recipient's own erythrocytes become immunogenic and stimulate an immune response known as autoimmunization; most autoantibodies are IgG, and some fix complement. Autoantibody formation can occur at any time but occurs most frequently in patients who have already developed multiple alloantibodies. Alloimmunization usually limits the ability to find compatible blood for future transfusions and increases the risk for delayed hemolytic transfusion reactions, so efforts to avoid alloantibodies seem warranted.

Key Question

KQ27. In patients with SCD requiring transfusion, what are the most effective strategies to reduce the risk of alloimmunization or autoimmunization?

Summary of the Evidence

The systematic review summarized more than 60 longitudinal and cross-sectional studies, involving more than 6,000 participants, in which alloimmunization or autoimmunization was described in adults and children with SCD undergoing transfusion. Rates of alloantibody formation ranged from 6 percent to 85 percent, while autoantibody formation ranged from 4 percent to 10 percent. These studies provide incidence and prevalence data only, and none compared the effectiveness of preventive strategies.

Most alloimmunization developed against erythrocyte antigens in the Rh blood system (D, Cc, Ee) and other minor blood groups (e.g., Kell, Kidd, Duffy). Phenotype matching of these antigens between transfusion donor and recipient may lower the alloimmunization rate, with a reported rate of 0–7 percent described in studies where strict matching criteria were employed.[408-411]

Iron Overload

Background

Transfused erythrocytes, whether administered through sporadic or repeated procedures, present an iron load to the recipient. The vast majority of the iron is carried by hemoglobin within the erythrocytes. As a rough calculation, 1 milliliter of erythrocytes contains approximately 1 milligram of iron, so for every 3–4 units of packed erythrocytes, 1 gram of iron enters the body. This process is clinically relevant, because adults normally have a total of only 4–5 grams of iron in their entire body, so this amount increases quickly after repeated transfusions. More importantly, there is no physiologic means to remove excess iron. Regulation of iron homeostasis normally occurs at the level of absorption through the hormone hepcidin, which inhibits the transport of gastrointestinal iron into the body. Because transfused blood represents iron that circumvents the normal pathways of iron regulation, this excess iron accumulates in tissues and can become pathological.

Hemosiderosis is a condition that reflects a large iron burden affecting normal organ function. The liver, pancreas, and heart are particularly vulnerable to iron overload. Chelation therapy can be used to remove excess iron. A number of different medications are used for chelation, but a thorough review of chelation dosing and management is beyond the scope of these guidelines. Deferoxamine is given by subcutaneous or intravenous route and leads to iron excretion through both urine and feces, whereas deferasirox is given orally once a day and removes iron primarily through the gastrointestinal tract. Deferiprone is taken orally three times a day and requires close monitoring due to the risk of agranulocytosis. Patients on monthly chronic transfusions typically receive chelation therapy to reduce iron burden, to attempt to normalize iron stores, and to avoid organ damage from hemosiderosis.[408,412]

Diagnostic Tools for Assessing Iron Overload

Changes in serum ferritin (SF) roughly correlate with iron loading, but the relationship is too inaccurate to use as a reliable method for evaluating iron status. Rather, SF is used as a biomarker to track qualitative trends of iron loading and chelation efficacy over time. Liver biopsy has been the gold standard in the diagnosis of iron overload but carries procedural risks and the possibility of sampling error. To avoid this invasive procedure, new diagnostic tools using MRI have been developed; these tools image the whole organ to quantify liver iron. Data are limited on the sensitivity and specificity of these new technologies to quantify liver iron in individuals with SCD. However, a significant body of literature supports the use of MRI as a substitute for liver biopsy for diagnosing iron overload in individuals with thalassemia.[413] There is no reason to believe that the quantification of tissue iron would be different in individuals with SCD, and there is literature where MRI was used as (1) a screening tool for identifying patients eligible to participate in a trial of chelation therapy (80 patients; Cappellini et al. 2010[414]), (2) a tool to monitor outcomes in a study of chronically transfused SCD patients (15 patients; Hernandez et al. 1988[232]), or (3) a tool in studies examining different chelation regimens (15 patients; Voskaridou et al. 2005; Cancado et al. 2009;[415,416] Levin et al. 1995; Ghoti et al. 2010[417,418]). Therefore, the expert panel considered the results in thalassemia patients when making recommendations for individuals with SCD.

Key Questions

KQ28. In patients with SCD undergoing chronic transfusion therapy, what are the effective strategies to reduce iron overload, and what are the most accurate diagnostic tests to estimate iron overload?

Summary of the Evidence

A total of 50 studies (2 RCTs, 35 observational, and 13 cross-sectional) plus 9 case reports related to transfusion-acquired iron overload were identified. One RCT[419] compared the use of deferasirox (oral) to deferoxamine (subcutaneous injections) in adults and children. The trial included 195 patients who were all iron overloaded (SF of at least 1,000 ng/mL, along with liver iron content of at least 2 mg iron/g dry weight of liver tissue in patients receiving simple transfusions, and 5 mg iron/g dry weight of liver tissue in patients receiving exchange transfusions) and demonstrated that the two approaches yielded similar results. The second RCT was the STOP trial,[408] which did not evaluate treatments for iron overload; however, enrolled children in this trial received chronic transfusion, which was associated with a rise in SF in the first year of the trial and which necessitated treatment with deferoxamine in several children. Twenty other observational studies compared different chelation agents, and all have consistently demonstrated reduction of iron overload as measured by several methods. Data regarding the comparison among the different chelating agents or against alternative approaches such as hydroxyurea and exchange transfusion are unavailable or of very low quality.

Most studies used an SF level >1,000 ng/mL to diagnose patients with possible iron overload (often an inclusion criterion in the study). However, some studies used cutoffs of 1,500 ng/mL or higher.[420,421] SF changes were nonlinear. Levels less than 1,500 ng/mL indicated mostly acceptable iron overload; levels of 3,000 ng/mL or greater were specific for significant iron overload and were associated with liver injury. Using a cutoff of 2,500 ng/mL, Karam et al.[412] reported that SF had sensitivity of 62.5 percent and specificity of 77.8 percent for identifying liver iron concentrations of 7 mg iron/g dry liver tissue or greater. One observational study defined iron overload by liver iron concentration of at least 2.2 mg iron/g dry weight of liver tissue.[422] Sufficient data were not found to allow the estimation of diagnostic accuracy of MRI, although many chelation studies used MRI findings as inclusion criteria.

Hemolysis

Background

Hemolysis (the breakdown and destruction of donor erythrocytes) can occur during or after a transfusion. It is important to note that the mechanism of transfusion-related hemolysis is immunologic, in contrast to the hemolysis of sickled erythrocytes, which is an intrinsic red cell defect. Most transfusion-associated hemolysis occurs 1 to 4 weeks after red cell transfusion and is called a delayed hemolytic transfusion reaction (DHTR). DHTR is related to immune-mediated mechanisms. The most common pathophysiology is preexisting or new IgG alloantibodies that bind to the erythrocytes and lead to accelerated clearance by macrophages in the extravascular compartment within the spleen, liver, marrow, and other parts of the reticuloendothelial system (RES). If the antibodies also fix complement, then erythrocyte destruction is further accelerated through lysis directly within the intravascular compartment. Both extravascular and intravascular hemolysis are manifest by shortened red blood cell survival, worsening anemia, and increased titers of antibodies found either on the erythrocytes themselves (positive direct antiglobulin, or "Coombs" test) or in the serum (positive indirect antiglobulin test) after the transfusion.

DHTRs can be associated with hyperhemolysis or bystander hemolysis. In this life-threatening complication of transfusion, patients will hemolyze not only the transfused blood but also their own RBCs, causing a profound anemia. This complication is recognized when the hemoglobin falls below pretransfusion levels and is often associated with reticulocytopenia and a positive direct Coombs test suggesting autoimmune destruction of RBCs.[423,424]

Clinicians should have a high index of suspicion for hemolysis after transfusions, and they should coordinate diagnostic testing with the appropriate blood bank or transfusion service. Avoidance of future hemolytic events depends on proper diagnostic testing and avoidance of offending erythrocyte antigens.

Key Question

KQ29. In patients with SCD undergoing transfusion therapy, what are the most effective strategies to reduce the risk of hemolysis?

Summary of the Evidence

Three RCTs, 17 observational studies, and 47 case reports were identified related to hemolysis in association with transfusions. The RCTs included more than 300 patients.[406,425,426] The studies described a prevalence of hemolytic reactions that ranged from 2 percent to 25 percent and an incidence of hyperhemolysis of 6 percent. There were no studies providing comparative effectiveness data on therapy. Descriptive studies reported successful management of the DHTR/hyperhemolysis (DHTR/H) syndrome with steroids, erythropoietin, and transfusion of phenotypically matched RBCs. The quality of evidence for management of these complications in SCD is very low, and data from transfusion in other populations may be indirectly applicable.

Hyperviscosity

Background

Transfusion of erythrocytes will increase the hematocrit of circulating blood, and increased viscosity could be problematic for patients with SCD. Avoidance of hyperviscosity is an important goal to prevent triggering a VOC.

Key Question

KQ30. In patients with SCD undergoing transfusion therapy, what are the most effective strategies to prevent and treat transfusion-associated hyperviscosity?

Summary of the Evidence

No studies were found that described the effectiveness of a particular preventive or therapeutic approach for hyperviscosity in SCD.

Recommendations for the Management and Prevention of Transfusion Complications

Although the literature summarized and described in the evidence table is of very low quality in most of the areas relating to transfusion complications, the expert panel opted to provide several recommendations based on extrapolation from transfusion literature on non-SCD populations, in vitro data, and the clinical expertise of the panel members. The panel members felt that clinicians in the field needed guidance to manage transfusion complications in patients with SCD and a comprehensive overview of this management.

Recommendations for Both Children and Adults

1. Obtain patient transfusion history to include locations of prior transfusions and adverse effects.
   (***Consensus–Panel Expertise***)
2. Ask the blood bank to contact hospitals where patient reported receiving previous transfusion therapy to obtain transfusion information.
   (***Consensus–Panel Expertise***)
3. RBC units that are to be transfused to individuals with SCD should include matching for C, E, and K antigens.
   (***Moderate Recommendation, Low-Quality Evidence***)
4. Consult the blood bank for a workup of a possible DHTR in a patient with any of the following signs or symptoms: acute anemia, pain, or jaundice within 3 weeks after a blood transfusion.
   (***Strong Recommendation, Moderate-Quality Evidence***)
5. In patients with SCA who are not chronically transfused and who are therefore at risk for hyperviscosity, avoid transfusing to a target hemoglobin above 10 g/dL (unless the patients are already on chronic transfusions or have low percent HbS levels).
   (***Moderate Recommendation, Low-Quality Evidence***)
6. In patients who receive chronic transfusion therapy, perform serial assessment of iron overload to include validated liver iron quantification methods such as liver biopsy, or MRI R2 or MRI T2* and R2* techniques. The optimal frequency of assessment has not been established and will be based in part on the individual patient's characteristics.
   (***Strong Recommendation, Moderate-Quality Evidence***)
7. Administer iron chelation therapy, in consultation with a hematologist, to patients with SCD and with documented transfusion-acquired iron overload.
   (***Moderate Recommendation, Moderate-Quality Evidence***)