Blood Transfusions to Patients with Sickle Cell Disease

People with sickle cell disease (SCD) have inherited a mutation in the beta-globin gene that changes the structure of their hemoglobin molecules. As a result, their RBCs have a short lifespan. Hemolytic anemia and acute bone pain—due to loss of blood supply to bones—are common in people with SCD. The RBC sickling process can also lead to trapped blood cells in the spleen (sequestration crisis) or lungs (acute chest syndrome), which can be fatal without treatment.

Blood transfusions are often used to treat patients with SCD. Transfusions can decrease blood viscosity, which tends to be high in these patients. Other transfusion goals are to increase RBCs’ capacity to carry oxygen and to decrease RBC sickling. However, the benefits of blood transfusions need to be weighed against the risks, such as TRALI and transmission of blood-borne pathogens. Furthermore, most patients with SCD have learned to tolerate their anemia, so they don’t need routine transfusions.

Experts don’t agree on how low a patient’s hemoglobin should be for that patient to require a transfusion. However, patients with SCD might benefit from a transfusion to increase RBC capacity to carry oxygen if they have severe anemia due to aplastic crisis, sequestration crisis or hyperhemolysis. Exchange transfusions are the only safe way to reduce a patient’s abnormal hemoglobin to a target level. Based on randomized controlled trials, exchange transfusions might be useful for preventing complications in patients with SCD during surgery or acute chest syndrome, as well as to prevent stroke.

Research hasn’t yet shown which patients need perioperative transfusions and what the safest and most effective transfusion strategies are for these patients. Some advisory committees recommend transfusions during procedures with a high risk of ischemia or hypoxia, such as cardiothoracic or vascular surgery. However, experts don’t usually recommend transfusions for vasoocclusive crisis due to trapped sickle cells in blood vessels. Supportive care using intravenous fluids, oxygen and analgesia is just as effective as transfusion for vasoocclusive crisis, while top-up transfusions can actually worsen symptoms, especially in bone.

Alloimmunization is a risk of transfusion in patients with SCD. This complication can be prevented through leukoreduction and matching patient and recipient blood for ABO, D, C, E and Kell antigens.

RBC Transfusions for Chest Complications in Sickle Cell Disease

Sickle cell disease (SCD) is the most common hereditary blood disorder in the world. Ruptured RBCs in people with SCD indirectly lead to constriction of blood vessels in the lung. As a result, about a third of people with SCD have pulmonary hypertension. This complication increases the risk of death and limits physical activity for these patients. Another SCD chest complication is chronic sickle lung disease (CSLD). About 5% of people with SCD have CSLD as a result of such contributors as pulmonary fibrosis and blocked blood vessels. People with CSLD have difficulty breathing, chest pain, trouble with exercise and episodes of acute chest syndrome. The symptoms of acute chest syndrome, caused by infections or sickle cells trapped in the lung, can include chest pain, coughing, breathing problems and fever. This syndrome is sometimes fatal.

The main therapies for chest complications of SCD are exchange and top-up RBC transfusions, hydroxyurea and hematopoietic stem cell transplantation. In exchange transfusions, the patient’s sickle cells are removed while donated sickle cell negative cells are transfused. A top-up transfusion involves giving RBCs to increase the patient’s hemoglobin level without removing the patient’s own RBCs. Exchange transfusions are much better for reducing the percentages of hemoglobin-S (abnormal hemoglobin that’s found in people with SCD) in patient blood than top-up transfusions.

The authors of this Cochrane review had planned to evaluate randomized controlled trials of long-term RBC transfusions to treat chronic chest complications in patients with SCD. However, they couldn’t find any studies that met all of their criteria. Randomized controlled trials are therefore needed to evaluate the effects of long-term transfusion therapy on pulmonary hypertension and CSLD in patients with SCD.


RBC Exchange in Patients with Sickle Cell Disease

Chronic RBC transfusions are often used to treat serious complications of sickle cell disease (SCD), such as stroke and acute chest syndrome. However, simple transfusions can lead to iron overload, as well as changes in intravascular volume and blood viscosity. Red cell exchange (RCE) avoids these problems, but it exposes patients to more RBC units per transfusion than simple transfusion. Patients who are exposed to large numbers of RBC units often develop RBC antibodies. Limited RBC matching for C, E and K antigens can decrease the risk of developing RBC antibodies as a result of chronic transfusions, but this approach doesn’t solve the problem completely.

A group of researchers from Houston, Texas, measured how often patients (mostly children) with SCD developed RBC antibodies after red cell transfusion therapy. Of the 93 patients, 78 had simple monthly transfusions and 15 had RCE. None of the patients on RCE developed antibodies to RBCs, compared to 1.5% of the simple monthly transfusion group. Eleven patients with antibodies continued RBC transfusions using RBC products that didn’t have the relevant antigens. Eight patients with antibodies stopped their transfusions and were treated instead with bone marrow transplantation or hydroxyurea.

Larger studies are needed to confirm that the rate of antibody formation is low after chronic RBC transfusions in patients with SCD. However, if the immunization rate is truly low, RCE could be used more often to treat the complications of SCD in children.

Platinum-based chemotherapy agents such as oxaliplatin and cisplatin can lower the bone marrow’s ability to make blood cells and cause drug-induced immune hemolytic anemia (IHA).

Two researchers from the Southern California Blood Services Region of the American Red Cross assessed immune reactivity of patient and donor samples. Plasma samples were incubated with RBCs coated with oxaliplatin or cisplatin, then agglutination of the RBCs was measured. Agglutination indicated the presence of antibodies to platinum. The RBCs came from healthy donors and patients who did not have drug-induced IHA.

Sixteen percent (19 of 121) of plasma samples from healthy donors agglutinated RBCs coated with oxaliplatin, and 7% (7 of 102) of the samples from these donors agglutinated both cisplatin-coated and oxaliplatin-coated RBCs. In cancer patients, 4% (2 of 50) of samples agglutinated RBCs coated with oxaliplatin. Development of antibodies in the healthy donors was somewhat surprising. The authors propose that these individuals might have developed antibodies to platinum as a result of exposure to the element in the environment. For example, catalytic converters in cars send it into the air, and traces of platinum chemotherapy drugs can eventually show up in food. Other sources include electronics, as well as glass and jewelry manufacturing. In the coming years, more healthy people might develop antibodies to platinum due to environmental exposure.

The authors warn that agglutination of these coated RBCs does not necessarily mean that a platinum-based chemotherapy drug caused a patient’s IHA, as agglutination may be caused by natural platinum antibodies. A better way to test whether these therapeutics are the cause might be to compare the levels of agglutination of treated and untreated RBCs in a solution of oxaliplatin or cisplatin.

Leger RM, Garratty G. Antibodies to oxaliplatin, a chemotherapeutic, are found in plasma of healthy blood donors. Transfusion. 2011; 51(8):1740–4.
Tranexamic Acid for Reduction of Blood Transfusions During Heart Surgery

Postoperative bleeding is a serious risk of heart surgery, and these patients often need extra blood transfusions or surgical re-exploration. Patients who have blood transfusions during or after coronary artery bypass graft (CABG) surgery have a higher risk of death over the long term than patients who don’t have transfusions. They are also more prone to infections, kidney failure and ventilator support. Heart surgery often involves cardiopulmonary bypass, which can stop platelets from functioning properly and increase both coagulation and fibrinolysis. All of these changes can lead to bleeding after heart surgery, especially in the elderly.

Tranexamic acid and ε-aminocaproic acid are often used to prevent bleeding after heart surgery. Studies have shown that tranexamic acid, in particular, can reduce bleeding and the number of needed transfusions following cardiac surgery in patients of all ages. However, previous studies haven’t examined the impact of tranexamic acid in elderly people after complex cardiac surgery. This report from a group of Norwegian researchers summarizes the results of a randomized controlled trial of the effects of tranexamic acid on bleeding after CABG or aortic valve replacement surgery in 64 patients, aged 70 years or older.

The placebo group had significantly more RBC transfusions than the patients treated with tranexamic acid. Thrombin antithrombin complex levels, which are signs of thrombin formation, were higher and D-dimer levels, a sign of fibrinolysis, were lower in the tranexamic acid group. However, similar numbers of patients in both groups had to be surgically re-explored because of hemorrhage after their first surgery (this may be because the study didn’t have enough statistical power to find differences in this rate). The results show that tranexamic acid can reduce the amount of RBCs that older patients need after complex heart surgery.

Preventing Reactions to ABO-Incompatible RBC Transfusions

Transfusions of ABO-incompatible RBC units can lead to sudden massive immune hemolysis of the transfused RBCs, hemoglobinuria and disseminated intravascular coagulation. These reactions can be fatal. In this review, experts from Marseille, France, discuss three research techniques in development to avoid transfusion reactions from the blood products of donors who have a different ABO blood type than the recipient.

Type O blood can be safely transfused into patients with A, B or AB blood. Therefore, one way to prevent transfusion reactions from ABO-incompatible RBC units is converting phenotype A, B and AB antigens into phenotype O. Studies have shown that Enzyme Converted Group O Red Blood Cell (ECO-RBCs) from type B RBCs treated with the galactosidase enzyme (extracted from coffee beans) survive in the bloodstream of people with type A, B or O blood. These patients have no early hemolytic immune reactions or side effects from the transfusions. However, so far, experts haven’t found an enzyme that can convert phenotype A antigens into phenotype O for RBC transfusions. Research is still needed to determine whether the ECO-RBC strategy prevents dangerous alloimmunization and is safe for routine clinical use.

A second potential strategy is masking the A or B antigen by treating RBCs with methoxyPEG (PEG). Studies in humans have shown that PEG treatment significantly lowers antigen visibility. However, no long-term data are available on what happens to RBCs treated with PEG. This technique still needs to be studied in large animal models and human trials before its usefulness for transfusion medicine can be known.

The third possibility is genetic engineering. One study used lentiviral vectors derived from HIV-1 to genetically modify CD34+ cells undergoing erythroid differentiation. After gene transfer, the erythroid cells had a different Kidd blood group from their original group. However, current gene transfer approaches probably won’t be useful for routine clinical purposes for a while because of technical drawbacks, including problems generating RBCs from CD34+ cells in vitro and doing the genetic manipulations. Although safe and practical methods aren’t yet available to create RBCs using genetically manipulated stem cells or cells derived from selected donors, this approach seems to be the most promising one.


HLA Mismatches in Cord Blood Transplantations

Most cord blood transplants from unrelated donors involve grafts with at least one mismatched antigen. Almost all of these transplants have involved a bidirectional mismatch, meaning that both the donor and recipient had the mismatched HLA antigen. Some mismatches are graft-versus-host (GVH)-only, meaning that the donor has two identical alleles at an HLA location, the patient has two different alleles at that location or only one patient allele matches the donor’s alleles. Other mismatches are rejection-only, in that the patient has two identical alleles and the donor has two different alleles (one of which matches the patient’s alleles) at a given locus.

In a study of 1,202 adults and children who had a cord blood transplant, bone marrow engraftment was faster and treatment failure rates were lower in patients with a GVH-only mismatch graft than those with a bidirectional mismatch. In contrast, the failure rates of rejection-only mismatches were higher than those of bidirectional mismatches. Moreover, patients with these transplants who had cancer had a higher risk of relapse, even if the transplanted cord blood engrafted. Therefore, the direction of a cord blood mismatch has important consequences for the patient’s risk of poor engraftment, relapse and death after transplantation.

**Allergic Reactions to Platelet Transfusions**

About 1–3% of patients who receive a transfusion with a blood product, especially one involving a large volume of plasma, develop an allergic transfusion reaction (ATR). Symptoms of these reactions range from itchy skin to hives, fainting and shock. This study compared ATR rates from split apheresis platelet product transfusions in at least two recipients to ATR rates after all apheresis product transfusions (including transfusions of both split and non-split platelet products). The study included data from more than 4,500 cancer patients who underwent apheresis platelet transfusion, including 1,000 who received split products. The authors reasoned that donor or product factors are more likely to explain ATRs in both patients transfused with a split product. However, if a recipient factor is the main cause of ATRs, then the rate of ATRs from split products should be the same as from all platelet products.

Of the 630 ATRs involving split products, only 6 ATRs occurred in both recipients. In patients who had at least 10 transfusions, whether split or not, 30% had an ATR after at least 5% of their transfusions. These patients accounted for almost two-thirds of ATRs in patients with at least 10 transfusions. Therefore, an inherited susceptibility in some plasma recipients appears to explain most ATRs.


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**High-Titer ABO Antibody Screening to Prevent Passive Hemolysis**

Transfusions of platelets containing ABO-incompatible plasma can cause hemolytic transfusion reactions (HTRs). HTR risk is especially high in patients with a small blood volume and those exposed to large volumes of incompatible plasma over time, as well as after transfusions of donor plasma with high-titer ABO antibodies. To reduce HTR risk from plateletpheresis products, the authors developed a practical technique to screen all plateletpheresis donors for high-titer ABO antibodies. Using this technique, they tested samples of pooled A1 and B RBCs by mixing them with diluted plasma in buffered gel.

Most cases of HTR due to high-titer antibodies have anti-A or anti-B concentrations higher than 1 in 150. For this reason, the authors set a cutoff of 1 in 250. With this threshold, 25% of group O and 5% of group A platelets had high-titer ABO antibodies.

In the two years after the screening program began, the institution increased its annual platelet use, but didn’t have any platelet-associated HTRs. The study’s results show that a single gel test of pooled A1 and B RBCs can be used to screen all plateletpheresis donors, regardless of their ABO group and even if their ABO group isn’t known at the time of screening.

Why People Do and Don’t Give Blood

Since the 1950s, many studies have tried to find out what motivates or deters people from donating blood. However, researchers have had trouble combining the results of these studies for analysis, in part because the authors of the published studies used different names for the factors they examined. Also, previous studies tended to focus on a specific group of donors in a specific country or region, and whether these results could be generalized to other groups wasn’t clear.

Two researchers from the University of Melbourne, Australia, created a classification system of factors that affect decisions to donate blood. To develop this taxonomy, they systematically reviewed the published literature on the factors that influence people’s decisions about donating blood. They also measured the proportions of people who said that each factor affected their donation behavior.

The categories of factors that motivated people to donate blood included prosocial motivations (like altruism), personal values (such as religion) and indirect reciprocity (expecting a benefit from a third party in exchange for donating). Some of the groups of factors that discouraged people from donating were low self-efficacy (such as lifestyle barriers), ineffective incentives and negative experiences with donating blood. The factor that motivated most people to donate blood was the convenience of the blood donation center. Many people also decided to donate out of a desire to help other people, because of the collection agency’s reputation or the need for blood products, or out of gratitude after they or a loved one had received a blood transfusion. Some of the most common reasons for choosing not to donate blood were lifestyle issues (like work or other commitments) that made donating difficult or the belief that they couldn’t give enough blood or would lose too much blood.

Mortality Rates in Men and Women after Massive Transfusion

Massive transfusions of units containing high ratios of RBCs to plasma and platelets are often used to treat hemorrhage and prevent death in patients after a serious injury. However, studies haven’t investigated whether these ratios have different effects in men and women.

This study compared the impact of low (less than 1:2) and high (1:2 or higher) ratios of plasma or platelets to RBCs on death rates in 704 men and women who had a massive transfusion of at least 10 RBC units within 24 hours of an injury. The death rate within 24 hours and at 30 days was lower in men who had high-ratio transfusions than men with low-ratio transfusions. However, death rates were similar in women who had high-ratio and low-ratio transfusions at 24 hours and at 30 days. Thus, massive transfusions of high ratios of platelets or plasma to RBCs might help men more than women after a serious injury.


Transfusing Platelets from D-positive Donors to D-negative Patients

When pregnant women with D-negative blood have been transfused with D-positive blood, especially RBCs and platelets, they can develop anti-D alloimmunization. The fetuses or newborns of these women sometimes develop hemolytic transfusion reactions, hemolytic disease or both, unless the mothers were treated with Rh immune globulin.

Previous studies found that up to 20% of D-negative people form antibodies after transfusion with D-positive blood products. However, a recent study by Cid and colleagues found an anti-D rate of only about 4% in more than 300 patients transfused with D-incompatible platelets over 10 years. According to an editorial by Beth Shaz and Christopher Hillyer of the New York Blood Center, the Cid study results show that transfusions of D-positive products are safe in people with D-negative blood, except for women who might become pregnant.

Better apheresis technology and processing of blood components have lowered RBC contamination in platelet products. The much smaller RBC volume in apheresis products could help explain the lower anti-D rate in the Cid study compared to earlier reports. However, no studies have identified the anti-D rate of transfused apheresis platelet products.

The Cid study didn’t find any differences in the number of D-positive pooled platelet concentrates transfused in people with D-negative blood who did and didn’t develop anti-D.

Also, the total number of transfused platelet products had no relationship to patients’ anti-D risk. Based on these data, Shaz and Hillyer reason that the number of transfused RBCs and platelets and how often people are exposed to D antigens might not affect anti-D risk.


Admission Platelet Count in Trauma Patients

Only 2% of trauma patients with severe injuries need a massive transfusion (at least 10 units of packed RBCs over 24 hours) for hemorrhagic shock when they arrive at the hospital. But 40% of these patients die from their injuries, and half of these deaths occur in the first 24 hours. This study measured the impact of platelet counts at admission on death rates and packed RBC transfusions in 389 trauma patients who had a massive transfusion.

The odds of dying dropped by 17% at 6 hours and by 14% at 24 hours with each 50 X 10^9/L rise in platelet count at admission. Patients who had a platelet transfusion within the first 24 hours were 67% less likely to die than other patients. The higher the patient’s platelet count at admission, the lower the number of transfused packed RBC units he or she was likely to receive. The results show that even a normal platelet count might not be high enough for people who have had a severe trauma, so the transfusion threshold for these patients might need to be lower.


Risks of Infections from Transfusions after Donor Testing

Better strategies for choosing and testing blood donors have made the U.S. blood supply safer now than ever before. However, a few patients still get infections from transfusions of infected blood. To learn about these infections, researchers analyzed data on all American Red Cross blood donations since 1995. The American Red Cross tests blood for HIV, hepatitis B and C viruses, human T-cell lymphotrophic virus (HTLV), syphilis, West Nile virus and Chagas disease.

In 2008, markers of almost all infectious agents were more common in blood from first-time donors than repeat donors. In first-time donors, testing found fewer markers of hepatitis C virus and hepatitis B markers in 2008 than 2001, but the frequency of HIV markers didn’t change. The drop in hepatitis B virus markers was probably due to growth in the proportion of donors who have had the hepatitis B vaccine.

The number of new hepatitis C virus and HIV infections grew between 2000–01 and 2007–08. Possible explanations are increases in the transmission of HIV among some young male donors and of hepatitis C virus from certain health care procedures (such as endoscopy) in donors older than 50.

For allogeneic, whole-blood and apheresis blood donations from first-time and repeat donors, the residual risk (risk after donated blood was tested) of HIV, hepatitis C virus and HTLV transmission was less than 1 per 1 million donations in 2007–08. The risk of hepatitis B virus was about 1 per 300,000 donations, but this risk could shrink now that more sensitive tests are being used.

Making Transfusions Safer

Published reports show that mistakes happen in every step of blood transfusion. Some of the most common mistakes are transfusing incompatible blood, making transfusion decisions that aren’t based on clinical findings and lab test results, and not monitoring patients for transfusion side effects or not managing any side effects that happen.

**Ways to avoid mistakes in transfusions include:**

- Training by transfusion nurses or other experts for all staff involved in transfusion
- Developing performance standards for transfusion safety and making sure that staff use the standards
- Using new technologies, like barcodes with handheld computers to identify patients during bedside transfusion checks

Transfusions of the wrong blood products are one of the main causes of death and injury due to transfusions. Therefore, an important step in preventing blood transfusion errors is to make sure that the patient is getting ABO-compatible blood. Errors leading to ABO-mismatched transfusions often happen when the patient is incorrectly identified during the bedside check just before the transfusion. Mismatched transfusions can also happen when labs test the wrong patient sample or make technical mistakes when identifying the blood products that the patient needs.

Blood transfusions are expensive and can cause complications. Thus, patients should receive transfusions only when no other options are available to treat or prevent clinical problems caused by low levels of blood cells or plasma components. Documenting blood cell and plasma deficiencies helps make sure that transfusion therapy is based on objective measurements. Even in patients with the same clinical features and for the same types of surgery, hospitals give transfusions of different amounts of blood products. Also, transfusions often don’t raise hemoglobin levels enough to improve the patient’s recovery from surgery. It might therefore be possible to reduce blood products use without any negative effects for patients.

A centralized transfusion center is a transfusion medicine model that can promote good clinical transfusion practice. In this model, a central facility stores blood products and has a reference lab for several hospital blood banks. Member blood banks can get advice from the central facility’s transfusion medicine specialists.

Continuing education is an important component of the career of all blood bank professionals. The American Red Cross is pleased to offer online and on-site learning opportunities to our valued hospital partners. Through the SUCCESS™ program, participants can earn SUCCESS CEU credits recognized for the recertification and licensure of laboratory professionals or AMA PRA Category 1 credits™ for physician Continuing Medical Education (CME) requirements. New courses are added to the SUCCESS website (success.redcross.org) on a regular basis. Examples of courses include:

**Basic Problem Resolution: A Case Study (CEU)**
This program will provide the opportunity to recognize aberrant test results in the initial testing of a blood bank sample. A step-by-step process used to resolve these results is discussed. The fundamental approach presented is not only appropriate for this scenario, but for all situations involving unexplained reactivity in initial blood bank testing.

**What's New with Granulocyte Transfusions (CEU and CME)**
Issues related to granulocyte transfusions are reviewed, including indications for transfusion, ordering products and administration. Product-related issues, including regulations, product dose and donor safety are covered. Future research efforts are highlighted.

**Serological Techniques Used in Antibody Identification**
Multiple techniques useful in assisting in antibody identification beyond the initial panel results and resolving ABO discrepancies are presented. These techniques include the use of: enhancement reagents, prewarming, neutralization, saline replacement, enzyme treatment and antibody titration.

Please visit success.redcross.org to learn more.

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