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On Our Cover

Endurance trapped in ice—

A photograph by Frank Hurley of the Endurance, the three-masted barquentine used by Ernest Shackleton when he led the ill-fated Imperial Trans-Antarctic Expedition from 1914 to 1917. As seasonal temperatures fell, the ship became trapped in and was ultimately crushed by pack ice. Stranded, Shackleton and his crew, with extraordinary effort and near-miraculous fortune, survived. In this issue, seven comprehensive sickle cell programs address the transfusion management of their patients in an effort to lessen the complications of sickle hemoglobin; the increased rigidity of red blood cells, much like liquid water becoming ice, plays a role in much of the unfortunate pathology of the disease.
Transfusion protocols for patients with sickle cell disease: working toward consensus?

G.M. Meny

While the exact number of individuals with sickle cell disease (SCD) in the United States is not known, it is estimated that SCD affects 90,000–100,000 Americans and occurs among 1 out of every 500 African-American births and among 1 out of every 36,000 Hispanic-American births. Improvements in therapy reduced mortality rates by up to 68 percent, particularly among young patients with SCD 0–3 years of age. However, the average life expectancy is estimated to be 53–60 years of age. Thus, further improvements in therapy are required to reduce morbidity and mortality and increase the life expectancy for these patients. What role does red blood cell (RBC) transfusion play in the care of patients with SCD and are transfusion medicine specialists doing all they can to minimize the complications of transfusion?

RBC transfusion plays a major role in the management of many of the acute and chronic complications of SCD, including anemia, acute chest syndrome, stroke, and pain crisis. Transfusion complications can include iron overload, infectious disease transmission, and volume overload. Some complications, such as alloimmunization and hyperviscosity, may be found more frequently in patients with SCD than in the general population. Alloimmunization results in delays in obtaining compatible blood and in increased incidence of delayed hemolytic transfusion reactions. A 10-year retrospective review reported alloimmunization rates as high as 29 percent in transfused pediatric patients with SCD and 47 percent in transfused adult patients with SCD when partial or extended RBC antigen matching was not performed. The use of antigen-matching protocols can reduce, but not eliminate, the risk of antibody formation.

The National Institutes of Health (NIH) recommends that a RBC phenotype (ABO, Rh, Kell, Duffy, Kidd, Lewis, Lutheran, P, and MNS at a minimum) be obtained on all patients with SCD older than 6 months. In addition, patients should be transfused with leukocyte-reduced, “antigen matched” RBCs or RBCs matched for C, E, and K to limit development of antibodies. These recommendations, developed by those who care for patients with SCD, are not universally followed when transfusing these patients. The Centers for Disease Control and Prevention (CDC) notes that while SCD is a “major public health concern,” individuals with SCD have less access to comprehensive medical care than patients with other genetic disorders, such as cystic fibrosis. Laboratories tend to vary in the transfusion protocols they follow when treating patients with SCD. A survey from the College of American Pathologists (CAP) found that only 37 percent of laboratories perform a RBC phenotype on nonalloimmunized patients with SCD and only 75 percent of these laboratories select phenotype-matched (most commonly for C, E, and K) units when transfusing.

In 2006, the editors of Immunohematology invited authors from several comprehensive sickle cell centers to describe their donor recruitment and transfusion management protocols. As Shulman noted in his introduction, it was interesting to review these articles for their discussions on the use of phenotype-matched donor blood for transfusion, given the lack of consensus on this issue, and on subsequent alloimmunization. The majority of programs reported providing CEK phenotype-matched blood. One program provided CEK phenotype-matched blood only after a patient developed his or her first RBC antibody. The extent of antigen matching for alloimmunized patients varied among the programs. Of interest, only one program described the use of molecular methods to predict the phenotype of either the patient or the donor. Data on the frequency of RBC alloimmunization were usually not provided, although one program reported a rate of approximately 5 percent.

I am pleased to welcome four authors from 2006 and three new authors to this issue of Immunohematology. The authors were asked to focus on a description of their transfusion management protocol rather than their donor recruitment protocol. Information requested included the use of phenotype- or genotype-matched blood in routine and emergency transfusion situations; donor RBC selection including age of transfused blood, cytomegalovirus (CMV) seronegative vs leukocyte reduced, irradiated, and hemoglobin S tested; and outcome data, including allo- and auto-antibody formation, cost, or clinical benefit. It is interesting to read the articles and particularly note the role that molecular testing is playing in the transfusion management of patients with SCD. Transfusion medicine specialists can play an important role in
extending these practices from the comprehensive sickle cell centers into the community.

References


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Antigen-matched red blood cell transfusions for patients with sickle cell disease at The Johns Hopkins Hospital

M.S. Karafin, R.S. Shirey, P.M. Ness, and K.E. King

There are a large number of patients with sickle cell disease (SCD) in the Baltimore metropolitan area. In 2009, the Centers for Disease Control and Prevention revealed that SCD affects 1 of every 500 African Americans, and that more than 70,000 people in the United States are reported to have the disease. The Maryland Department of Health and Mental Hygiene reports that African Americans make up almost 30 percent of the population of Maryland, which represents the fourth largest percentage (after Mississippi, Louisiana, and Georgia) of African Americans in the United States. Additionally, in Baltimore, African Americans represent 63.7 percent of the population according to the 2010 Census. Approximately 80 infants with SCD are born in Maryland each year, and of these, 47.5 percent live in the Baltimore area. Between July 1, 1985, and June 20, 2006, a total of 1680 babies with a sickling disorder requiring follow-up were identified through newborn screening. If all of these patients survived to age 65, there would be approximately 3520 patients with SCD older than 21 years of age living in Maryland. However, SCD remains associated with significant morbidity and mortality, and consequently, only 1700 adults with SCD were estimated to live in Maryland in 2006. The Hospital Discharge Database of the Maryland Health Care Commission revealed that from 2000 to 2005, there were 13,724 hospital admissions for adults with SCD, with an average length of stay of 4.94 days, and a total cost of $97 million.

The Johns Hopkins Hospital has separate adult and pediatric hematology services. The Sickle Cell Center for Adults is a center dedicated to providing both health and social services for adult persons with SCD who predominantly live in the Baltimore and Washington, D.C., areas. The center is now in its third year of operation and provides regularly scheduled outpatient visits, screening for hydroxyurea eligibility, genetic counseling, 7-days-a-week outpatient pain management, education, wound care, and social services. Since opening, the center has treated 611 total and 485 active adult patients with SCD. The center is an honorary chapter of the national Sickle Cell Disease Association of America.

The center has a full-time hematologist devoted to the care of persons with SCD. There are also several other adult hematologists within the division with expertise in SCD who serve as a backup for the center’s medical director. The center also has full-time physician assistants who address both acute and chronic medical issues and act as a liaison to other medical specialists throughout the hospital. Additionally, the center has developed a relationship with the emergency room to decrease waiting times for patients with SCD and has established continuity of care through follow-up appointments in the clinic (see http://www.hopkinsmedicine.org/hematology/sicklecell/).

The pediatrics department has nine full-time and part-time faculty members, four of whom have a primary research interest in SCD. The pediatric hematology division at The Johns Hopkins Hospital is a National Heart, Lung, and Blood Institute–funded Basic and Translational Sickle Cell Research Center. All children with SCD have a primary hematologist for long-term care as an outpatient, but their daily inpatient care is managed by a designated attending hematologist on service. There is also a weekly 2-hour SCD multidisciplinary care conference for inpatient and outpatient management issues.

Lastly, since 2007, the Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins Hospital has been actively investigating the use of bone marrow transplant as a treatment modality for patients with clinically significant SCD. Specifically, the center has been conducting a phase 2 trial investigating the combination of chemotherapy, total-body irradiation, and nonmyeloablative allogeneic hematopoietic stem cell transplantation on mortality and progression-free survival for patients with SCD. They have been recruiting both children and adults (2–70 years of age) who have a history of significant SCD–related morbidity, such as a previous stroke, acute chest syndrome, multiple red blood cell (RBC) alloantibodies, or osteonecrosis. Patient recruitment for this study is expected to continue through November 2012.
Transfusion Protocol and Donor Selection

The Transfusion Medicine Division and Hemapheresis and Transfusion Support (HATS) at The Johns Hopkins Hospital provide comprehensive RBC transfusion and apheresis support for the SCD population. In addition to providing routine RBC transfusions and RBC exchanges, they provide emergency RBC exchanges for severely ill pediatric and adult SCD patients at any time.

The current transfusion protocol at The Johns Hopkins Hospital for patients with SCD involves providing hemoglobin S (HbS)–negative, leukocyte-reduced, and ABO- and D-matched RBCs. Historically, when a new patient with SCD was first seen at Johns Hopkins, a serologically derived RBC phenotype was performed. However, in addition to serologic phenotyping, the transfusion service currently performs a DNA-based RBC antigen phenotype, making the procurement of a pretransfusion blood sample less critical in certain clinical situations. All phenotype information, both serologically derived and genotype derived, is archived and accessible via the transfusion medicine computer system. All blood intended for the SCD population is tested before release for sickling hemoglobin via a kit (Sickle-Sol®). The service neither specifically nor routinely provides ethnically matched, fresh (donor units collected within 14 days), irradiated, or cytomegalovirus-seronegative blood. There is no limitation to the age of the donor units. Moreover, phenotypically matched blood is not routinely provided if the patient does not demonstrate, or have a history of, an alloantibody or autoantibody. However, if an SCD transfusion patient does form an alloantibody or autoantibody, the known RBC phenotype is then used to assist in antibody identification. The transfusion service specifically avoids all antigens to which the patient has the corresponding alloantibody, and then prophylactically matches for all RBC antigens that are routinely associated with clinically significant alloantibodies, including those antigens in the following blood group systems: Rh, Kell, Kidd, Duffy, and MNS.

Within the last year, The Johns Hopkins Hospital transfusion service has initiated a new program to supplement the blood components provided by our routine blood supplier for the SCD patient population. This grant-funded initiative was modeled after several other successful programs throughout the country. The program involves recruiting healthy, HbS–negative, African American donors from the Baltimore community to donate apheresis RBCs to inpatient and outpatient individuals with SCD who require transfusion support. The goal of this program is to develop and maintain a registry of genotype-predicted phenotypes for both our SCD patient population and designated donors, and to actively match specific donors to transfusion-dependent SCD patients with a similar phenotype or genotype. This program is still in its infancy, and the transfusion service intends to evaluate its efficacy in the future. This program has been developed in association with ongoing efforts by the transfusion service and the clinical hematology services to serve as advocates for minority donation programs run by the American Red Cross.

Emergency Protocols

The Johns Hopkins Hospital transfusion service occasionally encounters some difficulty obtaining phenotypically matched blood for patients with SCD in a timely manner, especially when the need for blood is urgent, the patient has a rare or complex RBC phenotype, or large quantities are needed for an RBC exchange. The management of a patient with SCD in need of blood relies heavily on the clinical consultation between the attending hematologist and the attending blood bank physician. If the need for transfusion is deemed clinically urgent, and the patient is determined to need antigen-matched blood, every attempt is made to provide timely, fully phenotype-matched blood through the local blood provider. However, if this plan is determined not to be temporally feasible, blood is obtained that at least respects the patient’s known alloantibody(ies), and prophylactically matches as many additional antigens as the situation allows.

Warm autoantibodies also complicate the selection of appropriate blood for patients with SCD. As most if not all RBC units will be crossmatch incompatible in such situations, the transfusion service again makes every attempt to obtain phenotypically matched blood for the patient, even if the patient has no current or historic alloantibodies. Least incompatible blood is not routinely used at our institution, as phenotypically matched blood is thought to be as safe as the patient’s own blood. As time allows, the transfusion service will also perform adsorption studies to exclude new or previously unidentified underlying alloantibodies. However, this step may not be feasible before transfusion because of the urgent need for blood in these patients.

Protocol Outcomes

Formation of alloantibodies and autoantibodies to RBC antigens is a known significant complication for patients with SCD. The incidence of alloimmunization in patients with SCD ranges from 2 to 50 percent depending on the study.
Alloantibody formation is undesirable, as it creates the potential for serologic incompatibility, delays and complicates treatment plans, and increases the risk of delayed hemolytic transfusion reactions. By routinely determining the RBC antigen genotype or phenotype for all patients with SCD, we are optimally prepared to acutely manage the unexpected formation of either an autoantibody or an alloantibody. The rationale for this methodology is threefold. First, as a scientific community, we still do not have criteria capable of distinguishing those patients who are likely to form an alloantibody (an immune responder) from those who will not (an immune nonresponder). Although, on average, 25 percent of patients with SCD will form an alloantibody, studies indicate that up to 75 percent of patients will not, regardless of how many transfusions they receive.5,10 Moreover, previous studies have demonstrated that those who form an RBC alloantibody are at greater risk for forming additional RBC antibodies.11,12 Consequently, our transfusion service identifies those who are likely to be immune responders as those who have demonstrated the ability to form their first RBC alloantibody.4 Second, antigen matching is financially costly. Although each blood provider is different, hundreds of additional dollars can be spent per RBC unit to obtain phenotype-matched blood. This issue is of particular concern at our institution owing to the very large number of patients with SCD supported by our hospital. Lastly, particular RBC antigens or antigen phenotype combinations are rare, and consequently these phenotypes require prudent conservation. For example, Fy\(^{a}\) and Jk\(^{b}\) are associated with clinically significant alloantibodies. Although not rare individually, RBCs lacking both antigens are only found in about 9 percent of the general donor population.13 Not surprisingly, the number of RBC units lacking these two antigens is limited. Specifically requesting Fy\(^{a}\) and Jk\(^{b}\) RBC units for only those patients who have demonstrated alloantibodies or are immune responders, logistically, places less strain on the blood provider and the blood supply than requesting Fy\(^{a}\) and Jk\(^{b}\) blood for all patients lacking those antigens. In summary, unlike transfusion policies that require antigen-matched RBC units for all patients with SCD, our current transfusion protocol limits requests for phenotype-matched RBC units to only those patients who are likely immune responders, defends against the added cost of antigen matching, and limits the use of rare or uncommon RBC phenotypes.

Two small studies from our own institution have previously reported that none of eight chronically transfused pediatric patients with both SCD and at least one alloantibody developed a subsequent alloantibody or evidence of a delayed hemolytic transfusion reaction when transfused with multiple (median, 111.6 units per patient) prophylactic antigen-matched RBCs.10 Although not in patients with SCD, Shirey et al. similarly demonstrated that none of 12 patients who presented with warm autoimmune hemolytic anemia developed an underlying alloantibody despite being transfused with multiple prophylactic antigen-matched RBCs (mean, 15 units per patient).14 Moreover, despite 149 total transfusions, none of the 12 patients in this cohort developed adverse reactions to transfusion, and all of the study patients had the expected increases in hemoglobin and hematocrit values.14

Studies from other institutions support the efficacy of an extended antigen-matched RBC protocol. The incidence of alloimmunization in patients receiving this protocol is noted to be 0 to 7 percent, depending on the study.11,15,16 This incidence rate is notably less than the previously noted incidence of alloimmunization (25%) without antigen matching.11,12 The largest study to date using an extended antigen-matched RBC protocol revealed that in 99 patients evaluated during a 6.6 (median)-year period, only 4 (4%) developed a new alloantibody (anti-Le\(^{a}\), -Kp\(^{a}\), and two with anti-M) when individuals with partial D phenotypes were not included.11 Some institutions have used partial antigen-matching protocols such as matching for Rh and K to prevent the most common alloantibodies. These protocols have had reasonable success; however, previous studies have shown that alloimmunization to the unmatched antigens can occur.17–19

Although several studies demonstrate the efficacy of an extended antigen-matched RBC protocol, limiting the use of such a protocol until the formation of a first alloantibody is less well established. Unfortunately, retrospectively determining the effectiveness of our unique SCD transfusion protocol is difficult. Specifically, patients with SCD in the Baltimore metropolitan area often receive RBC transfusions acutely at local hospitals outside of the Hopkins system, many of which have transfusion policies very different from our own (i.e., no phenotype matching). As a result, alloantibody formation in the context of a patient who has been on a phenotype-matched RBC protocol at our institution cannot be definitively used as evidence of a protocol failure.

Since the transfusion service started routinely genotyping patients with SCD in the last few years, however, a cohort of 138 fully genotyped patients with SCD has been identified. This cohort is under active rigorous investigation, and future publications from our institution should be able to elucidate
the effectiveness of our protocol in this population, both in general and in terms of our newly initiated African American community donor program.

Summary

The Baltimore area has a large number of patients with SCD because of the large number of African Americans in our immediate urban community. The American Red Cross in our region, by fully understanding the needs of The Johns Hopkins Hospital and our unique patient population, has established a mechanism to readily provide fully, or close-to-fully, antigen-matched blood when requested. Consequently, our service determines the RBC genotype-derived phenotype of all patients with SCD before their first transfusion, and provides extended antigen-matched blood only when the patient demonstrates his or her first autoantibody or alloantibody. Although one small study at our institution and larger studies from other institutions suggest that extended phenotype matching may be effective at preventing delayed hemolytic transfusion reactions and alloimmunization in patients with SCD, the success of our unique program is an area of active investigation, and will be clarified in the coming years. In conclusion, although many SCD experts believe that prophylactic antigen matching should be the standard of care, the transfusion physicians at our institution remain unconvinced that phenotype matching RBCs for all patients with SCD, before they have shown the ability to make alloantibodies, is either cost-effective or medically prudent.

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Directed blood donor program decreases donor exposure for children with sickle cell disease requiring chronic transfusion


In children with sickle cell disease (SCD), primary and secondary prevention of strokes require indefinite regular blood transfusion therapy. The risks associated with repeated transfusions include alloimmunization and increased donor exposure. The Charles Drew Program is a directed blood donor program designed to lower donor exposure, decreasing the associated complications of transfusion; however, no evidence exists demonstrating the magnitude of the benefit to the recipient. Further, the use of extended red blood cell (RBC) antigen matching for C, E, and K has been well documented in a clinical trial setting but not extensively evaluated in a standard care setting. The goal of this study is to assess the effectiveness in reducing alloimmunization when matching for C, E, and K and the magnitude of the decrease in donor exposure in a directed blood donor program. The rate of alloimmunization and reduction of donor exposure were determined during the course of 1 year in a cohort of children with SCD who received regular directed donor blood transfusions. A total of 24 recipients were in the program, 16 females and 8 males, 4 to 20 years of age. During 2008, alloimmunization was 0 percent and donor exposure was reduced by 20 percent, compared with usual care. Extended RBC antigen matching has the same benefit as in a clinical trial setting for patients with SCD receiving blood transfusion therapy. Despite significant effort, we only achieved a modest decrease in donor exposure and cannot determine the immediate benefit of a directed blood donor program. *Immunohematology* 2012;28:7–12.

**Key Words:** sickle cell disease, blood transfusion, alloimmunization, donor exposure

Sickle cell disease (SCD) affects between 72,000 and 98,000 people in the United States.1 Approximately 1 in 2600 newborns and 1 in 400 African American newborns are born with SCD.1 Among children with sickle cell anemia (SCD-SS), strokes are one of the most devastating complications.2 By 14 years of age, approximately 11 percent of children with SCD-SS who are unscreened and untreated with prophylactic blood transfusion therapy will have an overt stroke, and 37.1 percent will have a silent cerebral infarct.3 Adams et al.4 demonstrated the relevance of transcranial Doppler (TCD) measurements for the primary prevention of overt strokes. Elevated TCD measurements are indicative of increased stroke risk; such testing should be used for early detection and initiation of treatment. The progression of neurologic complications typically results in regular blood transfusion therapy, proven to be effective in the primary and secondary prevention of overt strokes.5,6 In many large metropolitan areas or large referral centers, at least 20 or as many as 70 children with SCD receive regular blood transfusion therapy. Although red blood cell (RBC) transfusion therapy reduces the occurrence of strokes, it increases the risks of alloimmunization owing to repeated exposure to multiple blood donors. The persistent risk of alloimmunization for this susceptible population has been readily acknowledged, which has resulted in recommendations that individuals with SCD requiring regular blood transfusion therapy receive blood matched not only for ABO and D, but also for C, E, and K.7–13 However, College of American Pathologists surveys for RBC transfusion in patients with SCD in the United States show that transfusions are not generally matched for C, E, and K.14 Despite the common perception of the benefit of the strategy of extended RBC antigen matching for children with SCD who receive regular blood transfusion therapy, no randomized controlled trial has shown a direct benefit, and the relative merits of this strategy remain controversial.10

Blood banking centers that have minority recruitment programs have improved access to matched blood units.15–17 Within the St. Louis metropolitan area, the Charles Drew Program has been implemented to initially educate African Americans about the importance of blood donation and subsequently to increase African American blood donor activity and retention.2 The additional objectives of the program are to (1) provide phenotypically matched (C, E, and K), hemoglobin S (HbS)-negative, leukocyte-reduced RBCs to all pediatric patients with SCD-SS who require regular blood transfusion therapy for primary or secondary prevention of overt strokes; (2) to ensure that donated blood units are fresh with the goal of limiting the interval from collection to transfusion to a period of 5 days; and (3) to limit the number of donors to which each patient is exposed. The Charles Drew Program has been
successful in increasing the rate of African American donors in the St. Louis metropolitan area. However, the primary donor pool for individuals with SCD who receive regular blood transfusion therapy is predominantly non African American. This is a challenging disparity in blood donation practices among ethnic groups, with African American blood donors making less than 7 percent of donations in the United States, merely half of their proportion of the population, which is 13 percent. Before the inception of the Charles Drew Program in the St. Louis metropolitan area, 3 percent of the units collected were from African Americans and now approximately 5 percent are from African Americans. The annual total number of donated blood units increased from fewer than 4000 units to an average of more than 12,000 units among African American blood donors.

Despite the success of the Charles Drew Program in effectively raising African American blood donor rates, the program does not have any evidence of the direct benefit of matched donors to the target patient population, namely children with SCD receiving ongoing blood transfusion therapy. Specifically, there is no evidence for a decrease in the rate of alloimmunization and no evidence that there is a decrease in the donor exposure rate, the two major objectives of the program. However, in 2008, a concerted effort was made by the leadership of both the local and national American Red Cross (ARC) in collaboration with the Pediatric Sickle Cell Disease Team at St. Louis Children's Hospital to decrease the rate of donor exposure. The objectives of this study were to (1) determine the rate of alloimmunization in a directed blood donor program and (2) determine the rate of reduction of donor exposure for recipients of directed blood donor donations during the course of 2008.

**Materials and Methods**

This is a cohort study of all children who received blood donations from directed donors of the Charles Drew Program in 2008. This study was approved by the Institutional Review Board of the Human Research Protection Office at Washington University School of Medicine in St. Louis, Missouri, an affiliate of St. Louis Children’s Hospital. The Charles Drew Program is a directed blood donor program that serves patients with SCD at St. Louis Children’s Hospital located in St. Louis, Missouri. Charles Drew Program donors are unique to the SCD population because they volunteer to donate solely for this program and for a single patient in the program. Predominantly, but not exclusively, African American donors are recruited from blood drives that are at least 40 percent African American using the standard recruitment and communication guidelines of the Charles Drew Program.

Formative research in the form of focus groups was conducted with African American adults to guide efforts to recruit and retain program participants. The focus group discussion guides were designed around key constructs from the Health Belief Model—namely, perceived benefits and barriers to blood donation. Based on this research, the recruitment and retention of Charles Drew Program donors consists of intensive educational outreach that includes information about SCD and the importance, logistics, and safety of blood donation; testimonials from patients with SCD; one on one discussion with donors and volunteers at blood drives; and recruitment tables at the conclusion of church services. Among other findings, the research indicated that appealing to altruistic motives on the part of blood donors could lead them to decide to participate in the program. There is at least one dedicated recruiter at the ARC committed to recruiting Charles Drew Program donors. Recruited blood donors are asked if they would agree to have their blood samples tested for compatibility with a patient in the Charles Drew Program. All RBC transfusions are leukocyte reduced. Additionally, all of the units transfused are phenotypically matched for C, E, and K in addition to ABO and D as supplied by the ARC, Missouri-Illinois Blood Services Region. After phenotyping, if donors are found to be a match for a particular patient, they are asked if they would agree to donate solely for a single patient with SCD. Charles Drew Program donors are asked to commit to donating blood two to three times per year, within 7 to 10 days of their matched patient’s scheduled transfusion date, for a period of 2 years. Retention strategies include reminder telephone calls near the recipient’s scheduled transfusion and an annual luncheon for the Charles Drew Program donors, sponsored by the ARC, to acknowledge the donors and their direct impact on the SCD community.

**Statistical Analyses**

Descriptive statistics were used to illustrate the age and sex of the recipients. The number of new clinically relevant alloantibodies divided by the total number of transfusion units provided for the entire cohort during 12 months was calculated to determine the rate of minor RBC alloimmunization. We calculated the percent of reduction in donor exposure by subtracting the number of donors from the number of blood units transfused and then dividing the remaining number of blood units by the total number of blood units transfused. For example, the reduction in donor exposure for Patient 1 (Table 1)
Directed blood donor program for children with SCD

Results

Demographics

A total of 24 children in the Charles Drew Program from St. Louis Children’s Hospital received blood transfusions between January 1, 2008, and December 31, 2008. The recipient blood transfusion history at St. Louis Children’s Hospital ranged from 24 to 216 units transfused. The recipients were from 4 to 20 years of age. There were 16 females and 8 males. Among the cohort, chronic transfusion therapy was initiated for 3 recipients because of pain while they were being transitioned to hydroxyurea, 3 recipients for silent stroke, and 18 recipients for overt stroke. The average interval between transfusions among all 24 recipients was approximately 39 days, ranging from 28 to 55 days. For all study recipients, the mean number of units used for blood transfusions during 2008 was 24 units, ranging from 6 to 49 units. The average age of the blood units on transfusion date was 7.4 days. All Charles Drew Program recipients receive either manual or automated RBC exchange transfusions for secondary prevention of overt stroke.20 Before the conduction of this study, a total of 4 (17%) patients had preexisting clinically relevant alloantibodies: 3 patients exhibited anti-K, 2 patients exhibited anti-C, and 1 patient exhibited anti-E. The data indicated that these alloantibodies developed before the patients participated in the Charles Drew Program.

Rate of Alloimmunization

Among the cohort, the rate of alloimmunization was 0 percent (0 clinically relevant alloantibodies formed after 580 units of blood were transfused during the entire year). During those 12 months, no recipients formed clinically relevant alloantibodies.

Decreased Rate of Donor Exposure

All 24 recipients of the Charles Drew Program from St. Louis Children’s Hospital had a reduction in the rate of donor exposure when compared with the expected numbers of donor exposures in the absence of a directed blood donor program. As a direct result of the program, the average reduction in donor exposure was approximately 20 percent, ranging from 0 percent to 40 percent per patient enrolled in the program (Table 1).

Discussion

Blood donor programs and studies have been established to improve the quality of blood donations and to educate African Americans about SCD.17,21 However, to date, no direct benefits to children with SCD have been evaluated. To our knowledge, this is the first program that addresses the feasibility of both decreasing donor exposure and reducing the rate of alloimmunization for children with SCD who receive blood transfusion therapy. The Charles Drew Program is a concerted effort by the Missouri-Illinois ARC and the Sickle Cell Disease Team at St. Louis Children’s Hospital. During a 1-year period, the program decreased donor exposure by an average of 20 percent. Further, the program’s rate of alloimmunization was 0 percent (0 antibodies per 580 units transfused) versus 1.8 percent per unit transfused (45 new C, E, and K alloantibodies in 2461 units of blood transfusion therapy), the expected alloimmunization rate without an

Table 1. Difference between the potential number of donor exposures needed (based on the assumption of one donor per unit) and the actual number of donors exposed and the overall reduction of donor exposure

<table>
<thead>
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<th>Number of donors</th>
<th>Reduction of donor exposure (%)</th>
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<tr>
<td>Patient 24</td>
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<td>15</td>
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Total: 580
Total: 465
Average: 20
Furthermore, it is often a challenge to provide matched blood donations for children and adults who develop multiple alloantibodies. This challenge becomes acute and urgent in the event of a single life-threatening incident, such as multiorgan failure or acute chest syndrome with respiratory failure.

One potential advantage of the directed donor program that includes the extended RBC antigen matching over just an extended RBC matching program alone is a decrease in donor exposure. Significantly limiting donor exposure will decrease the likelihood of graft rejection in the event of hematopoietic stem cell transplant (HSCT), the only proven cure for SCD and definitive treatment for strokes in this patient population. The rate of graft failure or rejection is strongly related to the number of donor exposures from transfusions. Thus, minimizing exposure to multiple blood donors becomes increasingly critical as HSCT becomes a viable option for the cure of SCD.

The potential advantage of decreasing donor exposure in children with SCD is theoretical. We cannot determine whether an annual 20 percent reduction in donor exposure is sufficient to decrease the rate of graft rejection for the small group of children who elect to receive HSCT. None of our patients in the cohort have subsequently undergone an HSCT. As this is only the first year of a unified effort to decrease donor exposure, we are optimistic that we can improve and sustain this effort. Ultimately the added effort of blood donor services coordinated with the hematology service must be balanced against the perceived but unproven advantage of decreased blood donor exposure for the entire SCD pediatric population.

In the current cohort study, no individuals developed alloantibodies specific to the RBC antigens to which they were matched. However, as in the STOP Trial, it is possible for individuals to develop alloantibodies regardless of matching. We have no definitive explanation as to why these alloantibodies form, but several potential explanations exist. Participants of directed blood donor programs may develop relevant alloantibodies if they were transfused outside of the primary hospital where their transfusions are normally received. Also, C, E, or K antibodies can become undetectable and may later show up as a response to another immune stimulus. Additionally, technical errors by the person performing RBC phenotypes may occur, resulting in inaccurate interpretations and errors in transcription of the results. Further, weakly expressed antigens may render falsely negative phenotype results, a future component of antibody production.

In addition to the clinical benefits shown by this research, our study also provides preliminary evidence of the success of the Charles Drew Program in recruiting and retaining participants in a directed blood donor program. Although our study did not directly evaluate the success of the outreach

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**Table 2A. Reduction in the rate of alloimmunization in extended RBC antigen-matching programs compared with historical control patients**

<table>
<thead>
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<th>Historical control</th>
<th>STOP Trial</th>
<th>p value</th>
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<tr>
<td>Number of clinically relevant antibodies developed (C, E, and K)</td>
<td>45</td>
<td>4</td>
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<tr>
<td>Number of total blood units transfused</td>
<td>2461</td>
<td>1830</td>
<td></td>
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<tr>
<td>Rate of alloimmunization</td>
<td>1.8</td>
<td>0.21</td>
<td>&lt;0.001</td>
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</table>

**Table 2B. Reduction in the rate of alloimmunization in an extended RBC antigen-matching program with directed blood donations compared with extended RBC antigen matching alone**

<table>
<thead>
<tr>
<th></th>
<th>Charles Drew Program</th>
<th>STOP Trial</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of clinically relevant antibodies developed (C, E, and K)</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Number of total blood units transfused</td>
<td>580</td>
<td>1830</td>
<td></td>
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<tr>
<td>Rate of alloimmunization</td>
<td>0.00</td>
<td>0.21</td>
<td>0.260</td>
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program, specifically partnering with community churches, and informed by Health Belief Model constructs, the clinical results indicate that the programmatic and strategic decisions were successful and warrant additional study.

We have provided evidence that the benefit of extended RBC antigen matching is the same as in a clinical trial setting. However, for our second objective, we only achieved a modest decrease in donor exposure, despite significant effort by the ARC and the hematology services to decrease donor exposure. Further long-term evaluation of directed blood donor programs that target the reduction of donor exposure is warranted before this strategy is adopted by other hematology services and blood banks.

Acknowledgments

The authors would like to thank all of the families and the participants of the Charles Drew Program.

References


Transfusion protocol for patients with sickle hemoglobinopathies at Children’s National Medical Center

R.M. Fasano, W. Paul, E. Siegal, and N.L.C. Luban

Introduction

Children’s National Medical Center (Children’s National), located in the nation’s capital of Washington, DC, has a large international population because of its embassies and chanceries, and the World Bank, along with other government and international agencies and the presence of Howard University with its graduate schools with a large international student body. In fiscal year 2011 (FY11), the Sickle Cell Disease (SCD) Program at Children’s National provided comprehensive medical services from newborn diagnosis to age 21 years for more than 1200 children with homozygous SCD or another hemoglobin S (HbS) hemoglobinopathy. Of these patients, approximately 140 are on hydroxyurea therapy and 56 are on chronic transfusion therapy. The most common indication for chronic transfusion therapy is preventing primary and secondary stroke with cerebrovascular accidents (CVA; n = 15 or 26.8%) and abnormal transcranial Doppler ultrasonographies (TCD; n = 32 or 57.1%), followed by prevention of recurrent severe acute chest syndrome (ACS; n = 8 or 14.3%) and splenic sequestration. In addition, many children receive red blood cell (RBC) transfusions in the form of simple transfusion or erythrocytapheresis to abrogate sickle-related complications such as ACS, CVA, aplastic crisis, and splenic sequestration, or preoperatively to prevent postoperative sickle-related complications. Three transfusion modalities are currently used at Children’s National: simple transfusion, partial exchange transfusion, and erythrocytapheresis. Among the 56 patients with SCD on chronic transfusion regimen, 36 (64.3%) receive simple transfusion, 14 (25%) receive partial exchange transfusions, and 6 (10.7%) undergo erythrocytapheresis.

Children’s National’s Division of Transfusion Medicine (DTM) comprises the Blood Bank (BB), the Blood Donor Center (BDC), and the Blood Donor Processing Area. The DTM provides blood and blood products for transfusion to more than 230 patients per month with a wide variety of diseases and specialized transfusion needs. Blood and blood products are obtained from two sources: our own BDC and the Greater Chesapeake and Potomac region of the American Red Cross (ARC). In FY11, the BDC supplied approximately 45 percent of all RBC units transfused to patients treated at Children’s National through collection of more than 3000 RBC units, including 253 “buddy” units (see subsequent discussion). In the last two fiscal years, Children’s National’s BDC provided more than 53 percent of the RBC units required by chronically transfused hemoglobinopathy patients; 22.5 percent of these units were from buddy units.

SCD Transfusion Protocol

Donor and Recipient Testing

Children’s National donor samples are routinely tested according to U.S. Food and Drug Administration requirements for ABO, D, and infectious diseases. Blood samples from donors are also initially tested for HbS using a qualitative solubility test for the detection of sickle hemoglobin. Donors expressing AA hemoglobin are fully antigen typed using both serologic and molecular methods. Demographic and RBC phenotype data are entered into a database shared by the BDC and BB. In 2009, we initiated molecular testing using DNA analysis to predict RBC phenotypes to supplement serologic phenotyping. Molecular genotyping is performed on all African American donors based on optional self-identification during the screening process, and on all repeat donors of any ethnicity. Donors are then identified as potential buddies for patients who are chronically transfused or undergo exchange transfusion, and those on specific antigen-matching transfusion protocol. Further serologic confirmation of donor RBC antigens or absence thereof is performed when a recipient has a requirement for antigen-negative units either by demonstration of an antibody, history of an antibody, or protocol.

Recipient samples are tested for ABO and D using serologic methods, along with molecular genotyping. Additionally, serologic confirmation of the Rh type (C/c, E/e) is performed.
Extensive effort is made to perform molecular genotyping on all patients with SCD (and other chronically transfused patients) at first presentation to Children's National. Under hospital policy, BB staff reflexively identify the requirement for molecular typing for every patient with an admitting diagnosis of any sickle hemoglobinopathy (or thalassemia major) with the first request for type and screen, in addition to specific written orders by the treating clinical team.

**Unit Selection and Phenotype Matching**

All patients, regardless of diagnosis, receive prestorage leukoreduced RBC components. Irradiation restrictions for children with SCD are applied once the patient is listed for hematopoietic stem cell transplant (HSCT). Cytomegalovirus (CMV)-seronegative units are reserved for those children who are to undergo HCST after ensuring the CMV seronegativity status of their serum and that of the hematopoietic stem cell donor during pretransplant evaluation. Additionally, HLA antibody screening is performed on all children with SCD as part of pretransplant evaluation to preemptively detect and plan for the potential for peritransplant-related platelet refractoriness.\(^1\)

The SCD Program at Children's National has participated over the years in many National Heart, Lung, and Blood Institute–funded clinical trials involving transfusion. These include the Cooperative Study of Sickle Cell Disease (CSSCD),\(^2\) Stroke Prevention in Sickle Cell Anemia (STOP I and STOP II),\(^3,4\) Silent Cerebral Infarct Transfusion trial (SIT),\(^5\) and Stroke With Transfusions Changing to Hydroxyurea (SWiTCH),\(^6\) and currently participates in TCD With Transfusions Changing to Hydroxyurea (TWiTCH). Phenotypic matching for Rh (C/c and E/e) and Kell is performed for patients when such matching is required. Patients receiving buddy units are by definition provided phenotypically matched units for Rh (C/c, E/e) and K at a minimum. Patients not on research protocols do not receive phenotypically matched RBCs until they develop their first clinically significant antibody (anti-Le\(^a\), Le\(^b\), and -M excluded). After development of their first antibody, patients receive units phenotypically matched for C, c, E, e, and K. After the development of a second clinically significant antibody, they receive fully phenotypically matched units, defined as matched for Rh, Kell, Duffy, Kidd, and S (which is frequently excluded by necessity owing to its high frequency in the population).

**Buddy Program**

Initiated in 1998 and expanded in 2002, Children's National's Buddy Program was established to increase the number of African American donors who were phenotyped and who committed to frequent donations for our patients. We contact parents of all children on chronic transfusion and those being prepared for surgical admissions. We work with the family and friends of these patients to encourage blood donation for the broad community of children we serve. There is particular emphasis on the program for those with preexisting antibodies requiring fully phenotypically matched RBCs and for those children on protocols or on chronic transfusion. Once donors have identified themselves as being interested in becoming buddy donors, they are phenotyped and assigned as a designated buddy for one or more chronically transfused patients. On a weekly basis, an updated listing of patients for transfusion for the month is provided by the patient care team, and donors are recruited by the BDC or backfilled by our blood supplier. Non-buddy blood from our supplier is most often multiantigen-negative. In FY11, 30 of all 65 chronically transfused patients at Children's National received all or part of their transfusions from buddy units. Specifically, the Buddy Program, which consists of approximately 190 donors with an average of 14.6 (shared) donors per patient (1–58), supplied a mean of 40.7 percent of their total transfusion needs in the last two fiscal years.

**Special Circumstances**

RBCs phenotypically matched for C/c, E/e, and K are selected in advance for patients on chronic erythrocytapheresis and for emergency erythrocytapheresis when time permits. The decision to forgo phenotype matching is made by a blood bank director and is based on the clinical condition of the patient’s cardiorespiratory status, neurologic presentation, and potential for deterioration. Age of the components to be used for partial and full exchange is determined by institutional protocol, paralleling the concepts inherent in both neonatal exchange and massive transfusion. Older units (>14 days old) are used initially as they will be diluted by the patient’s blood volume and will be preferentially removed during the procedure. Fresher units (<10 days old) are used toward the end of the procedure as this represents the major fraction of RBCs remaining in the patient.

Patients with SCD are particularly susceptible to transfusion-induced autoantibody formation, especially individuals with multiple alloantibodies.\(^7,8\) These autoantibodies complicate conventional serologic determination of the patient's RBC phenotype and evaluation of allograft activities. In patients with SCD who express warm autoantibodies, the patient’s molecular genotype aids in providing extended phenotypically matched RBC products when the crossmatch
is incompatible with all available units, including autologous RBCs. Likewise, molecular genotyping also aids in confirming antibodies to high-prevalence antigens and in identifying and recruiting antigen-negative Children’s National donors. On rare occasions molecular genotyping of the patient has aided in the differentiation of an autoanti-e from an alloanti-e by demonstrating the presence of either a homozygous RH variant (i.e., (C)ce′/(C)ce′) or a heterozygous RH variant haplotype with cE in trans (i.e., (C)ce′/cE). In the former case, this information proved critical in acquiring future units from the American Rare Donor Program; in the latter case the information supported our approach to select R1R2 units for all further transfusions for this patient.

Program Performance

In FY11, a comprehensive audit of blood bank records at Children’s National demonstrated that a total of 1228 patients with hemoglobinopathy (SCD or thalassemia) had a type and screen performed in the blood bank at Children’s National during the preceding 10 years; 719 patients had received at least one RBC transfusion; and 178 patients have received greater than 15 lifetime transfusions at Children’s National. Of the 719 transfused patients, 124 (17.2%) had a history of one or more RBC alloantibodies, whereas 70 of 178 (39.3%) patients with greater than 15 lifetime transfusions were alloimmunized. Antibodies to Rh and Kell blood group antigens account for more than 75 percent of all alloantibodies formed. This rate of antibody formation is similar to what has been previously reported.29 As soon as an initial alloantibody, additional alloantibody, or autoantibody is identified, a series of events occur, which include sending a letter to the parents (and a copy to the patient care team) detailing the antibody(ies), the appropriate choice of RBCs, and a need to share this information with any health-care provider; requesting that the child wear an identification bracelet (MedicAlert bracelet; MedicAlert Foundation, Turlock, CA); updating information in the electronic medical record; and placing restrictions in the computerized laboratory information system with paper card file backup. Alloantibody and autoantibody information from teenagers at Children’s National who have made the transition to adult care is included as part of their detailed transitional medical history. Detailed letters with full phenotype and antibody history are prepared for families returning to their home country or on travel.

Evolving Phenotype Matching Policy at Children’s National

Routine molecular blood group testing via a beadchip method (Beadchip HEA, BioArray Solutions, Warren, NJ) was implemented in May 2009 at Children’s National. More than 2000 molecular analyses have been performed on 1460 donor and 610 patient samples, the majority of which are from patients with SCD. Molecular testing has aided the BDC in identifying and assigning buddies with matched Rh and Kell antigens to a subset of chronically transfused patients. Molecular blood group testing has also assisted in predicting donors with full phenotypically matched antigens for patients with multiple RBC alloantibodies or autoantibodies. However, recognizing that transfusion protocols that provide limited phenotype-matched units significantly reduce alloimmunization rates in patients with SCD,10–12 Children’s National plans to transition to a limited phenotype-matching transfusion protocol using its expanding molecularly tested donor pool in the near future.

In anticipation of this transition, an extensive audit of Children’s National’s BB database of molecularly tested donors and chronically transfused SCD (CT-SCD) patients was performed to assess the likelihood of success of providing the majority of Rh and Kell molecularly matched RBC units for CT-SCD patients from Children’s National’s BDC inventory. Likelihood of success was arbitrarily defined as the ability to identify a mean of five or more molecularly tested Children’s National–registered blood donors per CT-SCD patient. The number of Rh and Kell molecularly matched donors per patient was 256.7 ± 22.1 (SEM); however, after cross-referencing all shared donors with all other CT-SCD patients within and across ABO groups, the mean number of “unique donors” per patient was calculated to be 3.93 ± 0.31. The mean number of unique donors per CT-SCD patient with RBC alloantibodies was 2.56 ± 0.33 versus the mean number of unique donors of 5.09 ± 0.42 per CT-SCD patients without RBC alloantibodies (p < 0.0001). This audit confirmed that initiation of Rh and Kell molecular matching before formation of RBC alloantibodies in this population would likely result in a higher success rate of providing Rh and Kell molecularly matched RBC units internally from Children’s National blood donors for many CT-SCD patients, but would not obviate the need for supplemental blood supply from the ARC, especially in patients possessing certain rare phenotypes or expressing antibodies to high-prevalence antigens.
Unanswered Questions

Many unanswered questions remain with regard to transfusion support of patients with SCD, including determination of which patients will develop transfusional iron overload earlier and therefore benefit from earlier transition to erythrocytapheresis, whether there is a genetic predisposition to alloantibody and autoantibody formation in some patients with SCD, and the role molecular testing will have in providing molecularly matched RBC units and its impact on allosensitization and autosensitization. Future clinical and translational studies detailing the pathophysiologic mechanisms of alloimmunization and iron loading in SCD are needed.

References

Transfusions for patients with sickle cell disease at Children’s Hospital Boston

S.R. Sloan

Introduction

Children's Hospital Boston is a large pediatric medical center with 390 inpatient beds and several outpatient clinics. All transfusions of hospitalized patients with sickle cell disease (SCD) occur at the main hospital site in Boston. Outpatient transfusions take place at the main site in Boston and at a satellite clinic in Waltham, Massachusetts, which is about a 25-minute drive from the main Boston site. Approximately 180 patients with SCD are treated by Children's Hospital Boston annually. These patients are predominantly children. At age 18 to 21 years, patients are transitioned to an adjacent hospital that treats adult patients with SCD.

Red blood cell (RBC) units for transfusions at both sites are provided by one blood bank located at the main hospital in Boston. Children's Hospital Boston blood bank includes a blood donor center, transfusion service laboratory, and therapeutic apheresis unit. The apheresis unit performs RBC exchange transfusions for emergencies and for chronic transfusion therapy. Currently, approximately two RBC exchange procedures are performed each week. The blood donor center collects blood in a fixed site blood donor center adjacent to the main hospital lobby and from a bloodmobile that collects blood throughout eastern Massachusetts. The blood donor center collects enough blood to supply most of the RBC unit needs for Children's Hospital Boston. Although not a full immunohematology reference laboratory, the transfusion service laboratory performs many immunohematology laboratory tests and also has a molecular testing area that performs single-nucleotide polymorphism (SNP) analysis using the BioArray Solutions System of Immucor Corporation (Norcross, GA). Genotyping is performed on a large proportion of the blood donors.

RBC Selection Protocol

Children's Hospital Boston will use RBC units of any age for patients with SCD unless they also are in a category of patients who receive fresher RBC units, such as infants undergoing surgery. Except in emergencies, all RBC and platelet units at Children's Hospital Boston are irradiated, and patients with SCD receive irradiated units just as all other patients do. Patients with SCD receive RBC units that are negative for hemoglobin S (HbS). Although the BioArray molecular system tests for the HbS gene, the Sickledex (Streck, Inc., Omaha, NE) test is used to confirm that an RBC unit is negative for HbS.
All RBC and platelet units at Children's Hospital Boston are leukocyte reduced and considered cytomegalovirus (CMV) safe. In addition, some units are known to be serologically negative for CMV antibodies. Such units are preferentially provided to patients at higher risk for CMV infection such as hematopoietic progenitor cell transplant patients who are CMV negative. Patients with SCD are not considered at high risk for CMV disease and so do not preferentially receive CMV serologically negative units.

Children's Hospital Boston plans to test its RBC units for babesiosis using investigational tests and will attempt to have its entire RBC inventory tested for this disease. This will likely not be possible at all times. When there is an inventory of Babesia-tested and -untested RBC units, Babesia-tested RBC units will be preferentially provided to patients with SCD.

Emergency Protocols

If blood is emergently needed, blood untested for HbS may be transfused, at the discretion of the blood bank physician. Additionally, matching for the C, E, or K antigens may be skipped at the discretion of the blood bank physician. If no compatible blood is available, then Children's Hospital Boston will attempt to procure RBC units lacking the necessary antigens from other sources. In these situations, the blood bank physician will usually be in communication with the treating hematologist. If no crossmatch-compatible RBC units are available anywhere, or if the RBC units are needed before they arrive at the hospital, incompatible RBC units may be transfused. However, if the patient has clinically significant antibodies, for example to antigens in the Rh system, or if the patient has developed hyperhemolysis, then the recommendation may be to avoid the transfusion. Indeed, transfusions have successfully been avoided by providing supportive care for patients with SCD who have very low blood hemoglobin concentrations for extended periods of time.

If a patient has a warm autoantibody, underlying alloantibodies are identified with the use of adsorption techniques. In addition, the patient's predicted extended phenotype is determined by DNA methods. Such a patient is preferentially transfused with genotyped RBC units matched for several antigens. With this protocol, the blood bank knows the foreign RBC antigens to which the patient has been exposed and hence the potential alloantibodies that may develop.

Genotyping may also be performed on some select patients who do not have autoantibodies. These are determined on an individual case basis. In general, genotyping may help the laboratory investigation in patients with complex serologic test results. Also, genotyping can be extremely helpful in patients suspected of having Rh variant alleles based on serologic results. In these cases, Children's Hospital Boston will generally send out the specimen for further molecular characterization that cannot be provided by the standard BioArray chip.

Protocol Outcomes

Antibody development has generally been manageable with the protocols used by Children's Hospital Boston. Although we have not directly compared the antibodies developed under this protocol with antibodies that developed without D, C, E, and K matching, very few antibodies to these antigens have developed. The few patients who have developed antibodies in the Rh system usually have Rh variants or were transfused elsewhere. Specifically, a few patients developed antibodies that appeared to have a relative or absolute specificity for e antigen, and these patients were subsequently found to have variant RHCE alleles. One patient with SCD exhibited anti-D. Subsequent testing suggested that this patient had a partial RHD gene that was not detected before his transfusion of D+ RBCs. No patients with SCD in the past several years have developed panreactive autoantibodies. At least two patients have developed hyperhemolysis syndrome. The patients who developed hyperhemolysis did not have detectable autoantibodies, and one of the patients had no detectable antibodies against minor RBC antigens (negative antibody screen). The blood bank almost always has sufficient RBC inventory to avoid incompatibilities with any alloantibodies that have developed in patients with SCD, and few of these patients have developed autoantibodies. The main difficulties have been with patients with unusual RH alleles, some of whom have developed antibodies reactive with the Rh proteins present on most donor units. In rare cases, Children's Hospital Boston has needed to acquire RBC units from blood supplies for these patients. Although there are significant costs associated with genotyping, this testing has aided in the identification of valuable blood donors and greatly speeds the process of identifying antigen-negative RBC units. This improves the turnaround time, an improvement that is especially valuable for patients with SCD requiring emergent transfusions.

Summary

During the past decade, Children's Hospital Boston has had four changes affecting transfusion therapy for SCD patients:
1. A bloodmobile has helped increase blood collections. This could allow for more drives at locations with many African Americans, but attempts to date have not met the growing need.

2. Genotyping has allowed for predicting the extended phenotype of many RBC units and patients with autoantibodies.

3. Transfusion-transmitted babesiosis cases have increased, and Children’s Hospital Boston will soon be providing *Babesia*-tested RBC units.

4. The number of RBC units transfused to patients with SCD has increased as a result of studies finding the benefits of transfusion therapy in decreasing stroke risk. This has significantly impacted the inventory, making it difficult and sometimes impossible to provide RBC units matched for multiple antigens.

References


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The prevention and management of alloimmunization in sickle cell disease: the benefit of extended phenotypic matching of red blood cells

E.P. Vichinsky

The Northern California Sickle Cell Center at Children's Hospital Oakland offers comprehensive pediatric and adult services to 700 active patients with sickle cell disease (SCD). This includes 6900 outpatient visits and approximately 5000 inpatient days with an average length of stay of 4.7 days. Additionally, this includes a reference hemoglobin biology laboratory, a stem cell transplantation program, a 20-bed pheresis transfusion unit, an ambulatory center, and a centralized inpatient floor. Specialized services for nutrition, physiatry, pulmonary disease, brain function, transition program for adolescents, mental health services, and transfusion are included in our core program. The program focuses on prevention and treatment of complications. Prevention and treatment of brain injury is a major focus of the program. Approximately 6 percent of our annual transcranial Doppler ultrasonographs (TCDs) are abnormal, requiring transfusion therapy, and 16 percent of conditional TCDs eventually have converted to abnormal in our program, resulting in transfusion therapy. Preliminary studies suggest children with asymptomatic neuroimaging abnormalities have neurocognitive injury and both progress with time. Transfusion therapy is being studied to prevent this progression presently. Although more than 100 patients are receiving hydroxyurea therapy in our program, transfusion therapy remains a core treatment for many patients.

Chronic transfusion therapy is recommended for the prevention and for the treatment of many complications of SCD. Patients are transfused in a 17-bed ambulatory transfusion unit with weekend availability. All transfused patients are followed in a comprehensive transfusion program that offers red blood cell (RBC) pheresis, quantitative monitoring of body iron stores, and access to multiple iron chelators. Sixty pediatric patients and 40 adults are receiving chronic transfusions, with 40 patients receiving chronic RBC pheresis.

Transfusion Protocol

All patients upon enrollment in our program and before transfusion therapy undergo detailed pretransfusion testing for RBC antigens by serology and genotyping. Such genotyping has resulted in improved matching of individuals. Since 1994, all patients received blood matched for C, c, E, e, and K in addition to ABO and D. Once an antibody was made, phenotypic matching was extended to include Fy\(a\), Fy\(b\), Jk\(a\), Jk\(b\), S, s, M, and N. All patients commencing chronic transfusion have antibody formation and reactions monitored and recorded on a monthly basis. Each transfusion is preceded by a complete blood count, antibody screening, and hemoglobin S level. Patients initially undergo a routine antibody screening with a three-cell panel using a gel method (Ortho ID-MTS, Ortho Clinical Diagnostics, Rochester, NY). Positive screens trigger antibody identification with a ten-cell panel. When possible, absorption methods to detect autoantibodies are performed. Any antibodies with complex specificities are sent to the Blood Bank of the Pacific.

To maintain an extended phenotyping RBC transfusion program for patients with SCD, a minority donor recruitment program is supported. This program focuses on recruiting minority donors at alternative sites, such as churches, hospitals, and community events. Ethnic matching of units is not performed; however, all units are screened for sickle cell trait by solubility testing. Units are stored in CPDA-1 or Adsol S-1 (Baxter Corp., Round Lake, IL). There is no age requirement for the donor blood unit beyond standard life guidelines except in selected cases. Clinical data are developing that support the use of fresh blood. We are attempting to provide units less than 2 weeks old, but this is very difficult and has not been a requirement for most patients. All units undergo leukocyte reduction at the blood bank. Therefore, cytomegalovirus (CMV) screening, as well as irradiation of units, is not used except in the immediate pretransplant
management of patients. Although many programs irradiate RBCs, there is no evidence of benefit to patients with SCD, and there is a suggestion of shortened RBC survival.

Methods of Transfusion

Simple transfusions in the ambulatory setting, designed to maintain a pretransfusion hemoglobin (Hb) greater than 9 g/dL, is our standard protocol. When hemoglobin S (HbS) levels are high, the maximum Hb is maintained at less than 11 g/dL because of the risk of hyperviscosity. In chronically transfused patients with low HbS levels, maximum Hb levels as high as 12 g/dL are maintained. RBC pheresis is routinely used for initial stroke management and in the care of patients with high baseline Hb or difficulty in maintaining iron balance with iron chelation therapy.

Children’s Hospital Oakland Experience

Since 1990, we have prospectively been following the efficacy and complications of a chronic RBC transfusion. In 1992, we initiated a mandatory leukoreduced RBC program, and in 1994, we initiated a mandatory extended RBC matching for ABO, D, Cc, Ee, and K. In this program, once an antibody was formed, patients received units fully matched for Fyα, Fyβ, Jkα, Jkβ, S, s, M, and N. On rare occasions, patients who were unable to receive phenotypically matched units because of emergencies were transfused with D– K– RBC units. None of these patients developed antibodies. Before the initiation of phenotypically matched units, a retrospective review of our data indicated an alloimmunization rate of approximately 2 percent to 3 percent per unit of exposure. After initiation of our matching program, the overall alloimmunization rate fell to 0.05 antibodies per 100 units transfused. The alloantibodies that developed were anti-Lea, -M, -D, -C, -Kp, and -Rh. The workup suggested one patient was a partial D who typed as D+. At least three of these patients were transfused at outside institutions transiently. No patients developed progressive alloimmunization. Three autoantibodies occurred. These were warm IgG antibodies. All three autoantibodies were transient and did not prevent transfusion. We used the least incompatible units with complete phenotyping, and there was no evidence of hemolysis. In contrast, we did experience, in thalassemia, two patients with autoimmune hemolytic anemia that was associated with prior alloimmunization. Both patients were alloimmunized before enrolling in our program. One patient responded completely to Rituximab. The other patient showed transient elimination of the antibody when rechallenged with phenotype-matched units. This patient successfully underwent a stem cell transplantation using Alemtuzumab (Campath, Genzyme, Inc., Cambridge, MA) which resulted in complete elimination of the autoantibody. Before our matching program, hemolytic transfusion reactions occurred in 11 percent of our chronically transfused population. After the initiation of our extended RBC matching program, we have experienced only one hemolytic reaction. This patient was noted to have a lack of response to transfusion with a rising HbS level. The workup identified anti-Lea and -M, two antibodies that are generally not associated with hemolysis. The patient has been transfused for several years after this event and has not developed any transfusion complications.

Management of Complications

Prevention of Transfusion Reactions

Alloimmunization is one of the most important complications of transfusion therapy and SCD. The risk of alloimmunization to RBC antigens varies among individuals. There clearly are genetic determinants of patients with increased rate of antibody formation. Clinical and experimental data indicate that HLA molecules, proinflammatory cytokines (e.g., interleukin [IL] 1, IL-6, IL-8), costimulatory molecules (e.g., IL-10, transforming growth factor), and signaling molecules (e.g., cytotoxic T-lymphocyte antigen 4) associated with CD4-regulatory T cells mediate the response to alloimmunization. In addition, factors such as splenectomy, patient age, and disease subtype appear to be important. The two most important factors responsible for alloimmunization in patients with SCD are the number of transfusion exposures and the disparity in RBC phenotype between donor and recipient. With standard RBC matching, eventually 40 percent to 80 percent of recurrently transfused adult sickle cell anemia patients are alloimmunized. Our first approach to this problem is using limited and extended RBC phenotyping. Many of the antibodies are not persistent, and patients are receiving transfusions at multiple locations without information about their prior transfusion records. Unfortunately there is no central blood bank registry for patient reactions. The transfusion of RBCs to a patient previously sensitized to a transient clinically significant antigen is one of the most common causes of transfusion reactions. To address this, each patient is given a card or letter with his or her RBC phenotype and transfusion history. The patient is educated to present this information at each facility.

To prevent alloimmunization, all patients with SCD undergo complete antigen RBC typing. The RBC phenotype
is augmented by a genotype in patients who are chronically transfused.\textsuperscript{13} The genotype results enable the identification of patients with hybrid alleles at risk for undetected antibody reactions.\textsuperscript{14,15} For example, altered C antigens are present in as many as 20 percent of African Americans. These patients type serologically as C\textsuperscript+ but make anti-C.\textsuperscript{16} Patients without a history of immunologic reactions receive prospectively matched units for C, E, and K, as well as high-risk mutations uncovered with genotype testing.\textsuperscript{17} Once a clinically significant antibody develops, patients undergo extended matching. Duffy, Kidd, Lewis, and MNS are included. The reference blood bank is incorporated in a prospective transfusion program to plan for blood transfusion requests.

**Autoantibodies**

A positive direct antiglobulin test (DAT) is a common complication in transfused patients with SCD that results in significant clinical, laboratory, and financial problems.\textsuperscript{4,17} Inflammation, existing alloantibody, and genetic polymorphisms are risk factors. A positive DAT needs to be evaluated in the clinical setting. This includes laboratory evaluation for evidence of increased hemolysis and a detailed review of the transfusion history to rule out a primary immunization. A review of the patient’s drug history should be performed. Drugs such as cephalosporins are associated with positive DATs but rarely with hemolysis. Detailed evaluation of the positive DAT for IgG complement, strength, and temperature are necessary. Elution of the antibody and evaluation for a masked alloantibody are necessary. In general, the strength of the DAT does reflect the risk of hemolysis. Nonspecific, weakly positive DATs are commonly stimulated by chronic transfusions and are usually transient. Many patients have a polyspecific positive DAT that is negative on follow-up evaluation with monospecific reagents. Occasionally, they do have specificity. Our approach is to aggressively evaluate the patients with a positive DAT, including elution and specificity. If the patient shows no evidence of hemolysis or the DAT is weak, we continue the transfusion program using phenotypically matched units.

**Hemolytic Transfusion Reaction With Negative Evaluation**

Patients with SCD are prone to DAT-negative hyperhemolytic crisis.\textsuperscript{18,19} This occurs usually in chronically transfused patients who have clinical findings during an acute illness consistent with a hemolytic transfusion reaction. The cause of this serious event is unknown. Older, stored donor RBCs may accelerate hemolysis in patients with SCD by eryptosis with phosphatidylserine activation of an inflammatory hemolytic process. Clinicians have documented a bystander effect in which hemolysis of the transfused units induces hemolysis of the patient’s RBCs. Treating severe hemolytic transfusion reactions, whether DAT positive or negative, is difficult. Our approach is to avoid transfusions and use conservative therapy if possible. Lifesaving transfusions should not be withheld. Support of these patients is possible. We have used intravenous immunoglobulin (IVIG) therapy, high-dose erythropoietin, and steroids. Our success has been limited. Recently, we have found Rituximab to be effective in modulating the hemolysis.\textsuperscript{20}

In summary, transfusion therapy is increasingly used despite advances in treatment of SCD. As patients age, transfusion exposure significantly increases. Transfusion complications can be largely prevented by implementation of preventive strategies.\textsuperscript{21,22} These are not routinely implemented, largely because of concerns for cost. Detailed studies comprehensively evaluating the risk and benefit, focusing on cost, have not been completed.\textsuperscript{23} Several programs describe cost savings based on decreased need to search for specialty units because of fewer antibodies. Others have indicated the cost decreases because of the expansion of minority recruitment and the increased availability of rare antigen donors.\textsuperscript{24} However, patient safety should supersede cost savings. Therefore, our approach has been to focus on decreasing clinical morbidity. We have previously demonstrated that phenotypically matched units dramatically decrease the rate of alloimmunization. We are presently working to expand our donor pool, evaluate the benefit of genotyping, and identify clinically useful genetic risk factors for transfusion reactions.

**References**


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Transfusion practices for patients with sickle cell disease at major academic medical centers participating in the Atlanta Sickle Cell Consortium

A.M. Winkler and C.D. Josephson

The Atlanta Sickle Cell Consortium represents more than 2600 pediatric and adult patients with sickle cell disease (SCD) in the metropolitan Atlanta, Georgia, area receiving care at four major locations, each providing comprehensive care 24 hours a day, 7 days a week. Both transfusion services that support these sites use two levels of prospective phenotype matching to decrease the rates of alloimmunization. Although exact rates are unknown and are currently under investigation, alloimmunization occurs infrequently with the exception of chronically transfused SCD patients, who represent the minority of active SCD patients. With increasing availability, red blood cell genotyping will be used in the near future both for determination of predicted patient phenotypes and for provision of genotypically matched donor units. *Immunohematology* 2012;28:24–6.

**Key Words:** sickle cell disease, transfusion, phenotype matching

The Atlanta Sickle Cell Consortium represents more than 1000 adult and 1600 pediatric patients with sickle cell disease (SCD) in the metropolitan Atlanta area receiving care at four major locations. The Aflac Cancer Center and Blood Disorders Service of Children’s Healthcare of Atlanta (CHOA) offers the largest comprehensive pediatric SCD program in the country, serving 1675 active patients with SCD at three sites in metropolitan Atlanta: Children’s at Egleston (ECH), providing care for 573 active patients; Children’s at Scottish Rite (SR), providing care for 648 active patients; and Children’s at Hughes Spalding (HS), providing care for 454 active patients. With nearly a dozen pediatric hematology faculty members from either Emory University or Morehouse Schools of Medicine, the SCD program provides 24-hour acute care, health maintenance services, chronic transfusion services, patient counseling including follow-up from newborn screening, SCD education, and blood and marrow transplants for eligible patients. With outcomes exceeding the national average, the Aflac Cancer Center and Blood Disorders Service has performed more blood and marrow transplants for patients with SCD than any other program in the country. To date, more than 30 children with SCD have been cured through matched sibling bone marrow transplants with a 96 percent disease-free survival rate; the first successful unrelated cord blood transplant for SCD was also performed at CHOA. In fiscal year 2010, there were a total of 1402 inpatient hospitalizations (ECH, 605; SR, 500; HS, 297) and 7155 outpatient Aflac clinic visits (ECH, 2272, SR, 2622, HS, 2261) among all sites.

Once these patients reach adulthood (age 18 and older), their SCD care is most often transitioned to the Georgia Comprehensive Sickle Cell Center at Grady Health System (GHS), which was the first 24-hour comprehensive primary-care clinic for patients with SCD and has been focused on SCD management for more than 30 years. With 1035 active patients, the GHS Sickle Cell Center also provides complementary outpatient services including a clinic to ease the transition from pediatric to adult services, a multidisciplinary health maintenance clinic, leg ulcer and hydroxyurea clinics, chronic transfusion services, and other counseling and SCD management resources.

Transfusion support for patients with SCD at the previously referenced sites is provided by hospital transfusion services located at ECH, SR, and Grady Memorial Hospital under the medical direction of faculty from Emory University School of Medicine in collaboration with the American Red Cross (ARC) Blood Services, Southern Region, primary blood supplier of CHOA and GHS transfusion services. Although each blood bank has individual policies and procedures, the transfusion support of patients with SCD is similar across hospital systems.

**SCD Transfusion Protocol**

**Children’s Healthcare of Atlanta**

On receipt of a blood sample from an identified SCD patient, routine serologic testing including ABO and D typing and antibody detection and identification, if necessary, is
performed, similar to that for any potential transfusion recipient. When an SCD patient is initially seen at ECH or SR, a complete red blood cell (RBC) phenotype is performed by the ARC, which includes Rh, Kell, Duffy, Kidd, and MNS systems; phenotype testing is only performed if the patient has not been transfused within the last 3 months. The reference laboratory cost associated with an 11-antigen phenotype for C, E, c, e, K, Fy\textsuperscript{a}, Fy\textsuperscript{b}, Jk\textsuperscript{a}, Jk\textsuperscript{b}, S, and s is approximately $26 per antigen for a total cost of $286 per phenotype, but prices will vary by institution and reference laboratory. The CHOA protocol for transfusion of RBCs for SCD patients consists of two levels of prospective phenotype matching. The first category of matching is reserved for children who have not produced a clinically significant antibody and consists of prospective antigen matching for Rh (D, C, E, c, e), and Kell (K, k) (category 1). Once a child has become sensitized and produced clinically significant RBC antibodies (category 2), RBCs for transfusion are Rh (D, C, E, c, e), Kell (K, k), Fy\textsuperscript{a}, and Jk\textsuperscript{b} specific and must also be negative for any other antigens to which the patient has produced alloantibodies, if clinically significant (e.g., S, s, Js\textsuperscript{a}). In patients with a history of a warm autoantibody that is no longer detected by serologic testing, extended phenotype-matched units are provided. When the patient needs to be transfused, units are either ordered from the ARC Reference Laboratory or selected from the current stock of antigen-negative RBCs. RBC units for transfusion are all prestorage leukocyte reduced, hemoglobin S (HbS) negative, and as fresh as possible, preferably less than 14 days old; there is no requirement for irradiation. The cost for a RBC unit that is negative for C, E, K, and HbS is approximately $526, with an additional charge of approximately $80 for each additional antigen negative. This protocol is the same for all patients with SCD whether they are inpatients or outpatients and scheduled or urgent/emergent transfusions.

**Grady Health System**

When a patient with SCD is initially seen at either HS or GHS, the Grady blood bank performs a phenotype for C, E, c, e, K, Fy\textsuperscript{a}, Fy\textsuperscript{b}, Jk\textsuperscript{a}, Jk\textsuperscript{b}, S, and s, in addition to ABO and D typing, and antibody screening and identification if necessary. When a patient has been recently transfused, other methods may be needed to determine the patient’s RBC phenotype using either a hypotonic wash method or molecular studies; however, currently genotyping is typically reserved for patients who develop alloantibodies that do not seem physiologically plausible given previous phenotyping results or for patients who have developed uncommon alloantibodies for which no typing sera are available. When urgent RBC transfusion is necessary and a phenotype is unavailable at our institution, records from the ARC or referring facilities are often obtained. In the event the antigen profile is unknown, RBCs are emergently released that are negative for C, E, and K until a phenotype can be determined. Similar to CHOA, the GHS transfusion service has two levels of prospective phenotype matching. For patients with SCD who have not developed an alloantibody or autoantibody, prestorage, leukocyte-reduced, HbS-negative RBCs are provided that are matched for C/c, E/e, and K. As a cost-saving initiative, the Grady blood bank has developed a screening algorithm using automated RBC typing equipment to determine the C, E, and K status of donor units provided by the ARC, and we have successfully been able to limit costs and maintain an adequate inventory of units negative for C, E, and K. Once a patient has developed RBC alloantibodies or autoantibodies, RBC units are provided that are Rh (D, C, E, c, e), Kell (K, k), Fy\textsuperscript{a}, Jk\textsuperscript{b}, and S specific and negative for any other antigens to which the patient has produced clinically significant alloantibodies; S− units are only provided for patients older than 16 years of age. All RBC units are prestorage leukocyte reduced and HbS negative. There is no donor unit age or irradiation requirement.

**Emergency Protocols**

In cases of urgent/emergent transfusion needs, it may not be possible to complete antibody identification, especially for autoantibodies and complex serologic panels, or provide phenotype-matched RBCs; however, in these situations direct consultation of the blood bank medical director and clinical team is crucial. At times, it is possible to delay transfusion until serologic studies can be completed and partially or completely phenotype-matched units can be provided. At minimum, RBC units must be antigen negative for clinically significant alloantibody specificities. Of course there are exceptions to every rule, and it is most important to treat the patient before protecting the integrity of prophylactic measures; it may be necessary to emergently release RBCs before serologic studies or antigen matching can be completed for patients in life-threatening situations.

**SCD Transfusion Protocol Outcomes**

**Outcomes in Chronically Transfused Patients at CHOA**

Although alloimmunization rates of patients with SCD at CHOA have not been specifically measured, the occurrence of new antibodies is infrequent. Occasionally, patients are
transfused elsewhere without partial phenotype matching, and in this setting, patients have become alloimmunized. Alloimmunization data is available for the minority of patients with SCD who are chronically transfused at all three CHOA sites; however, it is currently being collected on all active SCD patients. Table 1 compares alloimmunization rates in the chronically transfused CHOA patients with SCD. Data for autoantibody formation is currently only available for the children at HS, and 6 (15%) patients have developed warm autoantibodies. Although less than 10 percent of patients are chronically transfused, even fewer undergo chronic erythrocytapheresis, which would be clinically beneficial. Given the current limitations of reimbursement for outpatient RBC exchange procedures in the state of Georgia, chronic RBC exchange transfusion is not a feasible option for most qualifying patients.

### Table 1. Alloimmunization statistics of chronically transfused patients with sickle cell disease

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of active patients</th>
<th>Number chronically transfused (%)</th>
<th>Number alloimmunized (%)</th>
<th>Number of patients receiving chronic RBC exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egleston</td>
<td>573</td>
<td>48 (8.4)</td>
<td>12 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Hughes Spalding</td>
<td>454</td>
<td>39 (8.6)</td>
<td>10 (25.6)</td>
<td>1</td>
</tr>
<tr>
<td>Scottish Rite</td>
<td>648</td>
<td>45 (6.9)</td>
<td>19 (42.2)</td>
<td>5</td>
</tr>
</tbody>
</table>

**Alloimmunization Rates of GHS Patients with SCD**

Of the 554 SCD patients with active blood bank records, 139 (25%) are alloimmunized and 52 (9%) have developed autoantibodies, thus requiring extended phenotype-matched units. However, this most likely represents an overestimation of alloimmunization as data were obtained from active blood bank records and many of these SCD patients were likely transfused prior to the initiation of prospective phenotype-matching programs. In addition, 20 of these patients have tracking notes in the blood bank information system that require a medical director’s consult before issuing any RBC units; these patients have either complex alloantibodies or a history of hemolytic or unexplained severe transfusion reactions. Under these circumstances, there is most often a conversation between the transfusion service medical director and hematology attending physician to weigh the risks and benefits of transfusion in this select group of SCD patients.

**Conclusions**

Two major academic medical centers in Atlanta, Georgia, CHOA and GHS, provide comprehensive care to more than 2600 pediatric and adult patients with SCD. The transfusion services that support these sickle cell centers of excellence use two levels of prospective phenotype matching to prevent alloimmunization. Although alloimmunization rates are currently under investigation, most patients are infrequently alloimmunized with the exception of chronically transfused patients with SCD. As genotyping becomes more widespread, increased adoption of genotyping patients with SCD and provision of genotypically matched RBC donor units will become a possibility; CHOA will embark on prospective genotype matching in 2012.

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Transfusion practices for patients with sickle cell disease at the Children’s Hospital of Philadelphia

S.T. Chou and D.F. Friedman

Key Words: sickle cell disease, transfusion, extended antigen matching, red blood cell genotyping

The Comprehensive Sickle Cell Center (CSCC) at the Children’s Hospital of Philadelphia (CHOP) provides routine and acute care for approximately 1000 patients with sickle cell disease (SCD). One hundred twenty patients with SCD are currently managed with chronic transfusion therapy, either by simple transfusion or by erythrocytapheresis to maintain a percent hemoglobin S (HbS) level of less than 30 or 50 percent, depending on the indication. The most common indication for chronic transfusion therapy at our institution is stroke prevention, either primary or secondary, followed by recurrent acute chest syndrome and splenic sequestration, and, less commonly, chronic cardiac disease or severe recurrent vaso-occlusive episodes. Many children receive acute or episodic red blood cell (RBC) transfusions when admitted to the hospital for parvovirus-associated aplastic crisis, acute chest syndrome, splenic sequestration, stroke, and transient ischemic attacks, or as preoperative therapy to decrease the risk of acute chest syndrome after general anesthesia.

Although transfusion therapy remains a mainstay for the treatment of acute and chronic complications of SCD, the risk of alloimmunization to minor RBC antigens continues to be a significant complication.1–5 Alloimmunization can have severe clinical consequences, not only because it can lead to significant delays in providing compatible blood, but also because alloimmunization in patients with SCD is associated with delayed hemolytic transfusion reactions (DHTTR), autoantibody formation, and hyperhemolysis (reviewed in Wahl and Quirolo6). At CHOP, we have implemented specialized transfusion protocols for patients with SCD to help decrease alloimmunization risk.

Transfusion Protocol

More than two thirds of alloantibodies formed by patients with SCD have Rh blood group (D, E, e, C, c) specificities, and the three most common alloantibodies in patients with SCD are directed against C, E, and K.4,7 Despite efforts to address this problem by prophylactic matching for C, E, and K (in addition to routine matching for ABO and D), about 10 percent of transfused patients with SCD still become alloimmunized.3,5 Our current practice for transfusion of patients with SCD is to match prospectively for C, E, and K, and to provide ethnically matched RBC units when possible. An extended RBC phenotype is performed on samples from all patients with SCD using an untransfused specimen, typically within the first year of life or at the first outpatient visit if transferring care from another institution. We determine ABO, D, C, c, E, e, K, Fyα, Fyβ, Jkα, Jkβ, M, N, S, s, Leα, Leβ, and P1 status by serologic methods. If a patient has been recently transfused, DNA-based methods are used to determine the predicted RBC phenotype. The extended phenotype is often helpful in guiding the serologic workup of new RBC antibody findings, as well as in prospective matching for additional minor antigens. For patients who have developed multiple alloantibodies or have a history of hyperhemolysis syndrome, we prospectively match RBC units for additional antigens, typically in the Kidd, Duffy, and MNS systems. This extended phenotype matching is performed on an individual case basis, taking into consideration the alloantibodies already formed, the antigens still at risk for antibody development, and the feasibility of the resulting extended match request.

Antibodies to low-incidence RBC antigens are also observed in our chronically transfused patients. Although these antigens are considered low-incidence because they occur in less than 1 percent of the general donor population, some are found at much higher incidence among African American donors.8 In many cases, reagents to screen RBC units for these antigens are not readily available. The blood supplier may be able to provide units from donors known historically to be antigen negative even if current donations cannot be screened. Two additional strategies are used to screen units for transfusion to patients with antibodies to low-incidence antigens. If the specificity is demonstrable in the
current serum sample based on reactivity with cells known to express the low-incidence antigen, then a negative anti-human globulin (AHG) phase crossmatch is accepted as an adequate screen for antigen-negative donor units. If the specificity is not demonstrable in the current serum sample, we may be able to use confirmed antibody-positive serum samples from the same patient that have been retained in frozen aliquots for this purpose. If none of these measures is available to screen for low-incidence antigens, RBC units must be issued with an unscreened status, for which our policy requires clinician acknowledgment by signature on a protocol waiver.

Matched blood for patients with SCD is most likely to be found among African American donors, whose RBCs more commonly lack C, E, K, S, Fy\(a\), Fy\(b\), and Jk\(b\) compared with Caucasian donors. In 1997, CHOP, the Penn-Jersey American Red Cross (ARC), and the local chapter of the Sickle Cell Disease Association of America initiated the Blue-Tag Program to direct blood from African American donors to children with SCD. Blood donors voluntarily self-identify as African American and agree to have their blood specifically support children with SCD by attaching a special blue tag to their donation. With 1200 to 1600 RBC units collected per month, these donors support the majority of transfusions for patients with SCD at CHOP and St. Christopher’s Hospital for Children. The primary reason a patient with SCD may not receive program units is the presence of alloantibodies that preclude an appropriate match from the Blue-Tag RBC inventory.

The issue of RBC alloimmunization within the Rh blood group system is greatly complicated by the genetic diversity of this locus within populations of African origin and the limitation of current serologic reagents to distinguish the many variant antigens. Altered D, C, and e often underlie complex Rh alloimmunization in patients with SCD. Many of these cases appear as apparent autoantibodies with relative specificities in the Rh system; however, molecular analysis reveals that many of these antibodies represent alloantibodies in the Rh system for which serologic reagents are not available. RH genetic testing can now be used in the clinical setting to detect altered *RHD* and *RHCE* in individuals at risk for producing antibodies to high-incidence Rh antigens. We use genotyping to resolve complex Rh antibodies, particularly for those patients who develop antibodies in the face of conventional antigen matching. Additionally, we obtain an *RH* genotype to supplement the RBC antigen profile for all chronically transfused patients with SCD.

One common variant *RH* allele in African Americans is the hybrid *RHD-CE-D*, which results from *RHCE* exons 3 through 7 replacing the region of *RHD* encoding D epitopes. The RBCs with this hybrid protein type as D\(–\) and C\(+\), but patients often develop anti-C when exposed to C\(+\) RBCs, and this can be associated with a D\(H\)T\(R\). In our blood bank, patients with the hybrid *RHD-CE-D* who lack an *RHCE* allele encoding conventional C receive C\(–\) RBCs to prospectively prevent anti-C production, consistent with the general policy for prophylactic C matching. Additional RBC matching for Rh variants is not performed because the clinical relevance of most variant alleles is unknown. Future studies to determine which additional variants should be included in prospective matching to prevent alloimmunization and hemolytic transfusion reactions is paramount, as molecular testing could provide superior outcomes.

### Donor RBC Selection Protocols

In addition to performing prospective C, E, and K antigen matching and providing ethnically matched RBCs when possible, we provide patients with SCD HbS-negative units that are screened by the blood bank via a rapid solubility test. Because the survival of transfused RBCs declines with storage, we provide RBC units collected within 21 days for patients on chronic transfusion programs. The goal is to improve RBC survival, maintain the desired HbS level between transfusion visits, and achieve longer transfusion intervals with concomitantly decreased iron burden. For episodic or acute transfusion of patients with SCD, we do not have a restriction on the age of the RBC units issued. The CHOP blood bank provides prescreen leukocyte-reduced cytomegalovirus (CMV)-safe blood to all patients, including those with SCD. Irradiation is performed on-site, just before issuance for transfusion, and is applied to the great majority of transfusions using protocols based on patient location and service. One exception is RBC units ordered on-call for the operating room for potential bleeding, in which the units are not irradiated unless medically indicated for the patient. In the case of SCD, on-call units would be irradiated. Many of our patients with SCD, particularly those who are chronically transfused, require washed RBC components owing to recurrent allergic or cytokine-mediated transfusion reactions despite premedications. RBC washing is performed on-site and within 24 hours of transfusion.

### Emergency Protocols

If emergent transfusion is necessary, the blood bank will issue uncrossmatched O\(–\) units or uncrossmatched type-specific blood (based on historical ABO type on at least two
prior specimens performed by the CHOP blood bank). Both protocols require a waiver signed by the treating physician. In addition, if time allows, C-, E-, and K-matched or antigen-negative uncrossmatched units can be requested by the medical team. Because we transfuse a large number of patients with SCD on a chronic basis, units known to be negative for C, E, and K are usually on the shelf and readily available for emergency transfusion. At CHOP, the emergency department and intensive care units have satellite blood component refrigerators that store O− RBC units that are unscreened for C, E, and K. These components have occasionally been used for patients with SCD who have life-threatening anemia requiring emergent transfusion. When uncrossmatched blood is transfused, whether issued by the blood bank or from the satellite blood component refrigerators, a retrospective crossmatch is performed with the patient’s specimen and a segment of the RBC unit that is retained in the blood bank. For patients with SCD, we would also retrospectively phenotype unscreened RBC units for their C, E, and K status to provide exposure information to the medical team.

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**Warm Autoantibodies in Patients With SCD**

It has been our experience that many patients with SCD who are chronically transfused form warm autoantibodies detectable for various lengths of time in the antibody screen. If a patient demonstrates a warm autoantibody in the serum, a sample is usually sent to our reference laboratory for allo- or auto-adsorption studies to evaluate for underlying alloantibodies. For chronically transfused patients, we typically arrange for blood samples to be drawn 2 to 3 days before a scheduled transfusion so that these adsorption studies can be performed in advance. In part because of proximity, our reference laboratory can also perform these studies within 6 hours for emergent situations. After the adsorption studies are completed, we request RBC units from our blood supplier that are matched for C, E, K, and any other antigens against which the patient has a past or current history of alloimmunization; crossmatches are performed in our blood bank, and the least incompatible units are issued for transfusion. Currently, we use the gel method for routine antibody screening and crossmatching. If a warm autoantibody is a repetitive finding for a chronically transfused patient, our blood bank may repeat the antibody screen using a low-ionic strength saline tube method, and if the warm autoantibody is not detectable by tube method, we often elect to perform subsequent antibody screens and crossmatches for that particular patient using the tube method.

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**Protocol Outcomes and Future Directions**

More than 5000 RBC units are transfused each year at CHOP to patients with SCD, which constitutes more than 40 percent of all RBC units issued by our blood bank. Selecting and providing the appropriate RBC units requires tremendous coordination between the CHOP blood bank, hematology service, apheresis team, and the Penn-Jersey ARC, which supplies the blood components. The risk of alloimmunization and DHTRs for patients with SCD has been significantly minimized by prospective partial phenotype matching in the Rh and Kell blood group systems. Additionally, the Blue-Tag African American blood donor recruitment program in Philadelphia has increased the local supply of ethnically similar RBCs whose blood group antigen profiles more closely match the patients’ needs. From a cost perspective, 4.7 percent of RBC units issued to patients with SCD were matched for a single antigen, 33 percent were matched for two antigens, and 61 percent were matched for three antigens, with the remaining matched for more than three antigens. This antigen matching increased the blood acquisition cost for the program by 65 percent over the base cost of RBC units. In addition, a handling fee for the Blue-Tag donor program added 3 percent to the overall cost for the program.

Most recently, RH genotyping of patients has improved our understanding of Rh antibody production in SCD and offers the possibility of eliminating further Rh alloimmunization if partnered with genotyping of donors. Commercial polymerase chain reaction–based technology is now available to detect the majority of RH variants, allowing high-throughput genotyping of donors and patients to select more accurately matched RBCs. Our goal is to characterize RH in all patients with SCD, to identify those who would benefit from RH genetically matched transfusions, and to improve transfusion outcomes by applying molecular methods in transfusion medicine.

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Specialist in Blood Bank (SBB) Program
The Department of Transfusion Medicine, National Institutes of Health, is accepting applications for its 1-year Specialist in Blood Bank Technology Program. Students are federal employees who work 32 hours/week. This program introduces students to all areas of transfusion medicine including reference serology, cell processing, HLA, and infectious disease testing. Students also design and conduct a research project. NIH is an Equal Opportunity Organization. Application deadline is December 31, 2012, for the July 2013 class. See www.cc.nih.gov/dtm > education for brochure and application. For further information contact Karen M. Byrne at (301) 451-8645 or KByrne@mail.cc.nih.gov

Manuscripts
The editorial staff of Immunohematology welcomes manuscripts pertaining to blood group serology and education for consideration for publication. We are especially interested in case reports, papers on platelet and white cell serology, scientific articles covering original investigations, and papers on new methods for use in the blood bank. Deadlines for receipt of manuscripts for consideration for the March, June, September, and December issues are the first weeks in November, February, May, and August, respectively. For instructions for scientific articles, case reports, and review articles, see Instructions for Authors in every issue of Immunohematology or on the Web at www.redcross.org/immunohematology. Include fax and phone numbers and e-mail address with all manuscripts and correspondence. E-mail all manuscripts to immuno@usa.redcross.org

Free Classified Ads and Announcements
Immunohematology will publish classified ads and announcements (SBB schools, meetings, symposia, etc.) without charge. Deadlines for receipt of these items are as follows:

**Deadlines**
- 1st week in January for the March issue
- 1st week in April for the June issue
- 1st week in July for the September issue
- 1st week in October for the December issue

E-mail or fax information to immuno@usa.redcross.org or phone (215) 451-2538
Online Specialist in Blood Bank (SBB) Certificate and Masters in Clinical Laboratory Management Program
Rush University
College of Health Sciences

Continue to work and earn graduate credit while the Rush University SBB/MS program prepares you for the SBB exam and the Diplomat in Laboratory Management (DLM) exam given by ASCP Board of Certification! (Please note acceptable clinical experience is required for these exams).

Rush University offers online graduate level courses to help you achieve your career goals. Several curricular options are available. The SBB/MS program at Rush University is currently accepting applications for Fall 2012. For additional information and requirements, please visit our website at: www.rushu.rush.edu/cls/

Rush University is fully accredited by the Higher Learning Commission [HLC] of the North Central Association of Colleges and Schools and the SBB Certificate Program is accredited by the Commission on Accreditation of Allied Health Education Programs (CAAHEP).

Applications for the SBB/MS Program can be submitted online at the following website: http://www.rushu.rush.edu/admiss/hlthadm.html

Contact: Yolanda Sanchez, MS, MLS(ASCP)℠SBB, Director, by email at Yolanda_Sanchez@rush.edu or by phone at 312-942-2402 or Denise Harmening, PhD, MT(ASCP), Director of Curriculum by e-mail at Denise_Harmening@rush.edu
Masters (MSc) in Transfusion and Transplantation Sciences  
at  
The University of Bristol, England

Applications are invited from medical or science graduates for the Master of Science (MSc) degree in Transfusion and Transplantation Sciences at the University of Bristol. The course starts in October 2012 and will last for 1 year. A part-time option lasting 2 or 3 years is also available. There may also be opportunities to continue studies for PhD or MD following the MSc. The syllabus is organized jointly by The Bristol Institute for Transfusion Sciences and the University of Bristol, Department of Pathology and Microbiology. It includes:

- Scientific principles of transfusion and transplantation
- Clinical applications of these principles
- Practical techniques in transfusion and transplantation
- Principles of study design and biostatistics
- An original research project

Application can also be made for Diploma in Transfusion and Transplantation Science or a Certificate in Transfusion and Transplantation Science.

The course is accredited by the Institute of Biomedical Sciences.

Further information can be obtained from the Web site:
http://ibgrl.blood.co.uk/MSc/MscHome.htm

For further details and application forms please contact:

Dr Patricia Denning-Kendall  
University of Bristol  
Paul O’Gorman Lifeline Centre  
Department of Pathology and Microbiology  
Southmead Hospital  
Westbury-on-Trym, Bristol BS10 5NB, England  
Fax +44 1179 595 342, Telephone +44 1779 595 455, e-mail: p.a.denning-kendall@bristol.ac.uk.
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- HLA-disease association typing
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For information, contact:
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at (503) 280-0210
or write to:
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or e-mail: demcoej@usa.redcross.org,
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Philadelphia, PA 19123-3594
ATTN: Janet Demcoe

National Reference Laboratory for Blood Group Serology

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ardp@usa.redcross.org

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“This book is fantastic! It’s more like reading an eyewitness account than a scientific textbook. It’s wonderfully readable, and a great addition to the books on blood groups.”

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The Discovery and Significance of the Blood Groups traces the history of the discovery of human blood groups—with all the feuds, frauds, and tales of generosity and genius. It reveals how each blood group emerged over time and how things stand today. It is a deft combination of academic exactitude and colorful memoirs. It includes illustrations, tables, figures, a glossary, a bibliography, and a detailed index.

The Discovery and Significance of the Blood Groups
- Contains the most up-to-date data on the structure and biology of each blood group
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The Discovery and Significance of the Blood Groups by Marion Reid & Ian Shine
Illustrated /Hardcover/ $36.00/ Full color/ 7.5X10/ 214 pp.
ISBN 978-1-59572-422-9

MARION REID, PhD, is one of the world’s foremost authorities on blood groups with a knowledge and expertise that colleagues describe as encyclopedic. In her distinguished career, she has coauthored books and nearly 400 articles and reviews, including the now classic Blood Group Antigen FactsBook, and Blood Group Antigens & Antibodies.

IAN SHINE, MD, is the author of the acclaimed books Serendipity in St. Helena: A Genetical and Medical Study of an Isolated Community (which Arthur Mournant recommended be read by every clinician and every medical student) and Thomas Hunt Morgan: Pioneer of Genetics.
Diagnostic testing for:
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- Posttransfusion purpura (PTP)
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Janet Demcoe (215) 451-4914
demcoej@usa.redcross.org
Sandra Nance (215) 451-4362
snance@usa.redcross.org

American Red Cross Biomedical Services
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700 Spring Garden Street
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Our laboratory specializes in granulocyte antibody detection and granulocyte antigen typing.

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- HLA (PRA) Class I and Class II antibody detection

For further information, contact:
Neutrophil Serology Laboratory (651) 291-6797
Randy Schuller (651) 291-6758
schullerr@usa.redcross.org

American Red Cross Biomedical Services
Neutrophil Serology Laboratory
100 South Robert Street
St. Paul, MN 55107

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**Becoming a Specialist in Blood Banking (SBB)**

**What is a certified Specialist in Blood Banking (SBB)?**

- Someone with educational and work experience qualifications who successfully passes the American Society for Clinical Pathology (ASCP) Board of Certification (BOC) examination for the Specialist in Blood Banking.
- This person will have advanced knowledge, skills, and abilities in the field of transfusion medicine and blood banking.

**Individuals who have an SBB certification serve in many areas of transfusion medicine:**

- Serve as regulatory, technical, procedural, and research advisors
- Perform and direct administrative functions
- Develop, validate, implement, and perform laboratory procedures
- Analyze quality issues preparing and implementing corrective actions to prevent and document nonconformances
- Design and present educational programs
- Provide technical and scientific training in transfusion medicine
- Conduct research in transfusion medicine

**Who are SBBs?**

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<td>614-253-2740 ext. 2270</td>
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<td>414-937-6271</td>
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<td>Clare Wong</td>
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<tr>
<td>Harwath Blood Center, University of Cincinnati Medical Center</td>
<td>Pamela Inglish</td>
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<td><a href="mailto:kkirkk@lsuhsc.edu">kkirkk@lsuhsc.edu</a></td>
<td><a href="http://www.mclno.org/webresources/index.html">www.mclno.org/webresources/index.html</a></td>
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<td>Lesley Lee</td>
<td>214-649-1785</td>
<td><a href="mailto:lesley.lee@utsouthwestern.edu">lesley.lee@utsouthwestern.edu</a></td>
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**How does one become an SBB?**

Background check and appropriate training.

**Who are SBBs?**

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**Contact the following programs for more information:**

Additional information can be found by visiting the following Web sites: www.ascp.org, www.caahep.org, and www.aabb.org

**Revised May 2012**
I. GENERAL INSTRUCTIONS
Before submitting a manuscript, consult current issues of Immunohematology for style. Double-space throughout the manuscript. Number the pages consecutively in the upper right-hand corner, beginning with the title page.

II. SCIENTIFIC ARTICLE, REVIEW, OR CASE REPORT WITH LITERATURE REVIEW
A. Each component of the manuscript must start on a new page in the following order:
   1. Title page
   2. Abstract
   3. Text
   4. Acknowledgments
   5. References
   6. Author information
   7. Tables
   8. Figures

B. Preparation of manuscript
   1. Title page
      a. Full title of manuscript with only first letter of first word capitalized (bold title)
      b. Initials and last name of each author (no degrees; all CAPS), e.g., M.T. JONES, J.H. BROWN, AND S.R. SMITH
      c. Running title of ≤40 characters, including spaces
      d. Three to ten key words
   2. Abstract
      a. One paragraph, no longer than 300 words
      b. Purpose, methods, findings, and conclusion of study
   3. Key words
      a. List under abstract
   4. Text (serial pages): Most manuscripts can usually, but not necessarily, be divided into sections (as described below). Survey results and review papers may need individualized sections
      a. Introduction — Purpose and rationale for study, including pertinent background references
      b. Case Report (if indicated by study) — Clinical and/or hematologic data and background serology/molecular
      c. Materials and Methods — Selection and number of subjects, samples, items, etc. studied and description of appropriate controls, procedures, methods, equipment, reagents, etc. Equipment and reagents should be identified in parentheses by model or lot and manufacturer’s name, city, and state. Do not use patient’s names or hospital numbers.
      d. Results — Presentation of concise and sequential results, referring to pertinent tables and/or figures, if applicable
      e. Discussion — Implication and limitations of the study, links to other studies; if appropriate, link conclusions to purpose of study as stated in introduction
   5. Acknowledgments: Acknowledge those who have made substantial contributions to the study, including secretarial assistance; list any grants.
   6. References
      a. In text, use superscript, Arabic numbers.
      b. Number references consecutively in the order they occur in the text.
   7. Tables
      a. Head each with a brief title; capitalize the first letter of first word (e.g., Table 1. Results of . . .) use no punctuation at the end of the title.
   8. Figures
      a. Figures can be submitted either by e-mail or as photographs (5 ×7” glossy).
      b. Place caption for a figure on a separate page (e.g. Fig. 1 Results of . . .), ending with a period. If figure is submitted as a glossy, place first author’s name and figure number on back of each glossy submitted.
      c. When plotting points on a figure, use the following symbols if possible: ○ ● △ ▲ ■ □.
   9. Author information
      a. List first name, middle initial, last name, highest degree, position held, institution and department, and complete address (including ZIP code) for all authors. List country when applicable.

III. EDUCATIONAL FORUM
A. All submitted manuscripts should be approximately 2000 to 2500 words with pertinent references. Submissions may include:
   1. An immunohematologic case that illustrates a sound investigative approach with clinical correlation, reflecting appropriate collaboration to sharpen problem solving
   2. Annotated conference proceedings
B. Preparation of manuscript
   1. Title page
      a. Capitalize first word of title.
      b. Initials and last name of each author (no degrees; all CAPS)
   2. Text
      a. Case should be written as progressive disclosure and may include the following headings, as appropriate
         i. Clinical Case Presentation: Clinical information and differential diagnosis
         ii. Immunohematologic Evaluation and Results: Serology and molecular testing
         iii. Interpretation: Include interpretation of laboratory results, correlating with clinical findings
         iv. Recommended Therapy: Include both transfusion and nontransfusion-based therapies
         v. Discussion: Brief review of literature with unique features of this case
         vi. Reference: Limited to those directly pertinent
         vii. Author information (see II.B.9.)
         viii. Tables (see II.B.7.)

IV. LETTER TO THE EDITOR
A. Preparation
   1. Heading (To the Editor)
   2. Title (first word capitalized)
   3. Text (written in letter [paragraph] format)
   4. Author(s) (type flush right; for first author: name, degree, institution, address (including city, state, and country) for other authors: name, degree, institution, city and state)
   5. References (limited to ten)
   6. Table or figure (limited to one)

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