Report

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

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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.[1] 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.[2] Additionally, in Baltimore, African Americans represent 63.7 percent of the population according to the 2010 Census.[3] 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.[2] However, SCD remains associated with significant morbidity and mortality, and consequently, only 1700 adults with SCD were estimated to live in Maryland in 2006.[2] 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.[2]

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 (Dade® Sickle-Sol®, Siemens Healthcare Diagnostics, Inc., Newark, DE). 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.[4] Least incompatible blood is not routinely used at our institution,[5] 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.[6–8]

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.[9,10] 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 supported the concept that extended phenotype matching can be a successful approach for preventing alloimmunization and delayed hemolytic transfusion reactions. First, King et al. 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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