Transfusion support of patients with sickle cell disease at the Children's Hospital of Philadelphia

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The American Red Cross (ARC), Penn-Jersey Region, Cooperative Sickle Cell Donor Program (CSCDP) began in September 1997 at the request of one of the clinical hematologists treating patients with sickle cell disease (SCD) at the Children's Hospital of Philadelphia (CHOP). The ARC Penn-Jersey Region now collects more than 1000 productive units of blood per month from donors who voluntarily participate in this program designed to attract African American blood donors. This program is successful because of the combined efforts of CHOP physicians, the ARC Penn-Jersey Region, the Philadelphia/Delaware Valley Chapter of the Sickle Cell Disease Association of America, and generous blood donors. The program currently serves two children's hospitals in Philadelphia. The keystone of the program is the blue tie tag that was developed by CHOP and ARC Penn-Jersey Region staff used to identify units in the program.

Over 1000 children with SCD are enrolled in the comprehensive sickle cell center (CSCC) at CHOP where they receive medical care during routine and acute illness visits. Approximately 115 children receive chronic transfusion therapy and have ongoing needs for "blue tag" units from the CSCDP. Primary and secondary stroke prevention is the most common indication for transfusion, followed by prevention of acute chest syndrome and acute splenic sequestration recurrences. Many children receive acute RBC transfusions to decrease the morbidity of SCD complications, such as acute chest syndrome and acute exacerbation of anemia, or as preoperative therapy to decrease the risk of acute chest syndrome following general anesthesia.

Transfusion Protocol

The CHOP protocol for transfusion of RBCs for patients with SCD consists of prospective phenotype matching for C, E, and K, and issuance of prestorage leukocyte-reduced "CMV safe," irradiated RBCs that are HbS negative. The HbS testing is done at CHOP using a rapid solubility test. In the event that a blue tag unit is HbS positive, it is transferred to another institution for use in their general inventory.

The practice of matching for C, E, and K, when phenotype-matched donor RBCs are needed for patients with SCD, is consistent with other hospitals' practices.[1] At CHOP, to determine the need for matching, each patient with SCD has an extended RBC phenotype performed using an untransfused specimen. If the patient has been recently transfused, other methods may be needed to determine the phenotype of the patient's RBCs. While a hypotonic wash method can be used to isolate HbS-positive RBCs (the patient's RBCs), molecular methods are useful for the detection and identification of variants of e and D that occur at a high rate in this population. In the event the antigen profile is unknown, RBCs are released that are negative for C, E, and K until a true phenotype can be determined.

For patients on chronic transfusion programs, many of whom are patients with SCD, our protocol calls for transfusing RBCs less than 21 days old at the time of transfusion. The rationale for this practice is that the in vivo recovery and survival of transfused RBCs decline with storage age and chronically transfused patients will have higher Hb values, longer transfusion intervals, and ultimately less transfusion iron loading, if fresher RBCs are used. It is not always possible to meet this

requirement if there are other constraints such as multiple antibodies or limited supplies. In addition, this freshness protocol is not applied to patients with SCD that have acute or one-time indications for transfusion.

Our SCD transfusion protocols support a very large RBC exchange program. We currently treat more than 50 patients who return to the apheresis unit for partial or complete RBC exchange every 3 to 4 weeks. Many of these patients are on prophylactic protocols for primary or secondary stroke prevention and require the percentage of HbS to be maintained at either less than 30 percent or less than 50 percent (for secondary stroke prevention in selected patients).[2] Patients receiving RBC exchange usually have peripheral access. In the event that peripheral access fails, a port that is suitable for use in apheresis is placed for access. Automated RBC exchange transfusion is preferred at our institution for patients with SCD requiring chronic transfusions to decrease total body iron burden, thereby preventing or forestalling iron overload.[3]

Selection of Protocol

Eighteen to 25 percent of all patients with SCD are alloimmunized because of RBC antigen frequency disparities between African American patients with SCD and European American blood donors. Because of the high frequency of alloimmunization in this patient population, all children with SCD have an extended RBC antigen phenotype performed in their first year of life, before their first RBC transfusion or at entry into the CHOP CSCC. With approximately two-thirds of the antibodies formed having specificities for antigens in the Rh or Kell systems, we adopted the practice of transfusing RBCs that are C, E, and K-matched. Multi-institutional studies conducted to determine whether RBC transfusions could decrease or prevent neurological and respiratory complications in patients with SCD have also adopted transfusion guidelines using C, E, and K-matched RBCs. The frequency of RBC alloimmunization in these studies was apparently reduced to a rate of 1 to 8 percent using phenotype-matched RBCs.[4,5] Those antibodies that did develop had specificities in the Duffy, Kidd, and MNS systems. Presently, we are analyzing the number of patients with SCD and alloimmunization and the number of delayed hemolytic transfusion reactions since the CSCDP began in 1997.

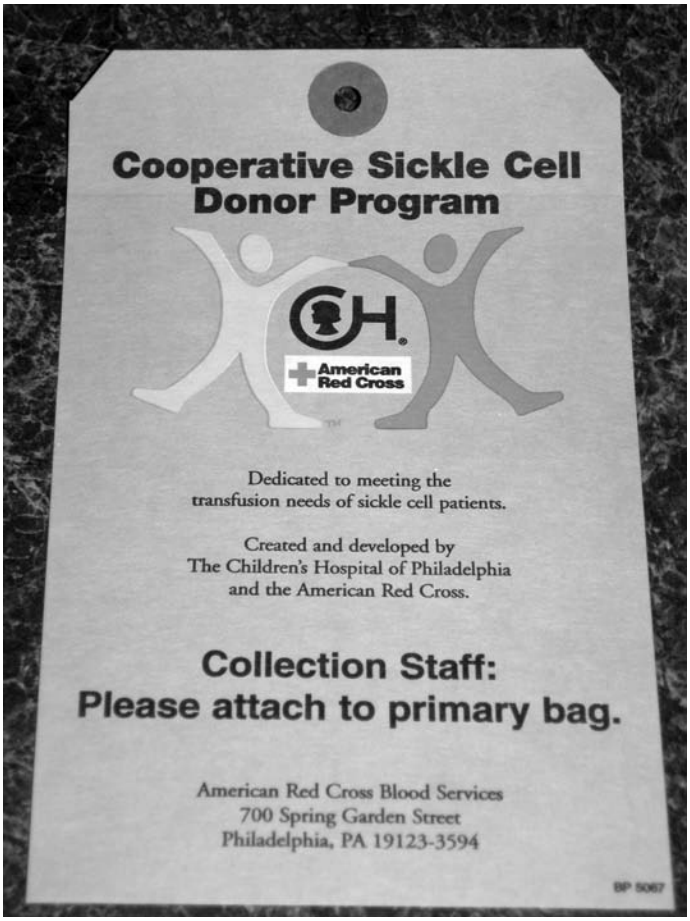
Summary of Data from the Program

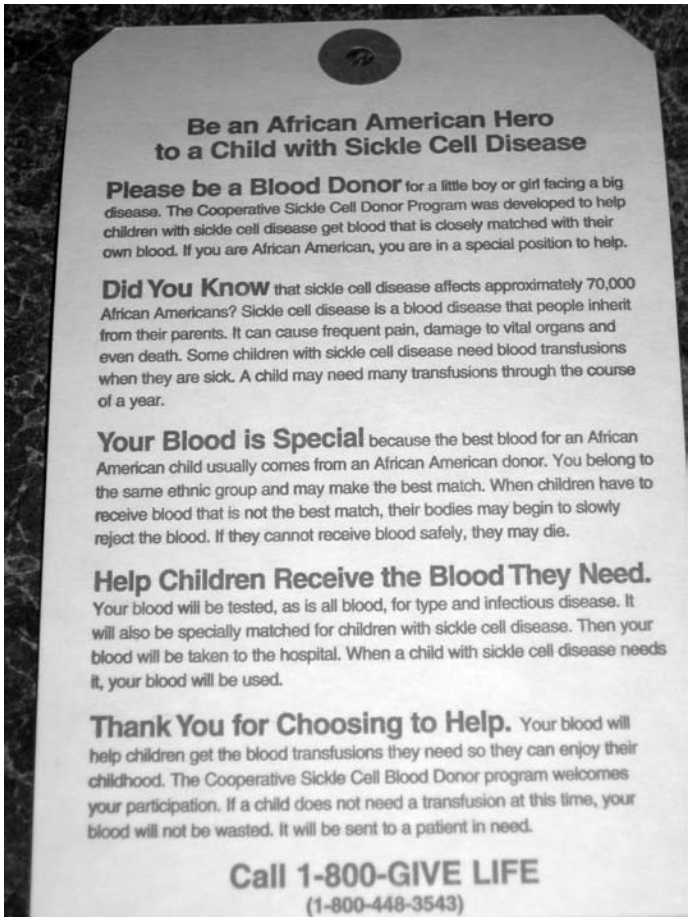
To provide an overview of this program, we reviewed the transfusion experiences of patients with SCD at our institution from 2002 to 2005. On the average, more than 3800 RBCs with blue tags were received per year, or 73 units per week. This represents 36 percent of all the RBCs received over this time period. These RBCs provided more than 16,000 transfusions over the 4-year period, about 58 percent of the total RBC transfusions. Of the blue tag units received, 92 to 93 percent were transfused. Interestingly, only 51 percent of these were transfused to patients with SCD; the remaining units were transferred into the general inventory and transfused to patients with other diagnoses. At CHOP, blue tag units are also routinely ordered and used for patients with thalassemia.

The range of transfusion exposures among the patients with SCD in this 4-year period was broad, with 66 percent of these patients receiving no transfusions, 19 percent receiving 1 to 9 transfusions, 9 percent receiving 10 to 99 transfusions, and 5.5 percent receiving more than 99 transfusions. About 70 percent of the transfusions, blue tag or general inventory, went to this latter group of very heavily transfused patients. These figures do not represent these patients' total lifelong transfusion history, only the experience of the 4 years reviewed.

Overall, only about 60 percent of RBCs transfused to patients with SCD came from the blue tag inventory, the remainder came from general inventory. Viewed from the patient's perspective, 137 of the 300 patients with SCD who were transfused in the 4 years reviewed, or 46 percent, received 90 percent or more of their units from the blue tag inventory; 93 patients or 31 percent received all of their transfusions from the blue tag inventory. No one patient of these 93 who were entirely supported with the blue tag inventory received more than 50 transfusions total and only 7 received more than 10. On the other extreme, there were 47 patients, or 16 percent of those transfused, who received 0 to 10 percent of their transfusions from the blue tag inventory, 37 of them receiving no blue tag units at all. This group of patients, who received no blue tag units over 4 years, included 3 patients who received a total of more than 100 units.

We also investigated 14 patients with SCD who, although they received more than 10 RBC transfusions, less than 10 percent of their blood support was provided with blue tag units. In nine of these cases,





additional antibodies including anti-S, -Jk^a, -Jk^b, -Js^a, -V, -f, -Co^b, and -Wr^a made it difficult to provide the patient's RBC needs from within the blue tag inventory. In two cases, the patient's RBCs were group B, D–; in two cases, R_2R_2 RBCs were needed because of auto-anti-e, and in one case, extended phenotype matching had been prescribed because of unexplained hemolytic transfusion reactions. It is possible that the diagnosis of SCD was not known to the blood bank in one case.

Donor Recruitment Process

There are more than 10,000 donors who have self-identified for the CSCDP. Demographic analysis of the program reveals a younger age group than the general donor population at the ARC in Philadelphia with the majority of donors between 19 and 29 years of age. In addition, because of the distribution of ABO groups, one-half of the donated RBCs are group O. When a donor walks into any collection site in the Penn-Jersey Region, there is a poster display showing a bright young child with SCD and the distinctive blue tie tags. The names and logos for CHOP and the ARC are displayed on the front of the tag as co-branding for the CSCDP. The back of the tie tag has information about SCD and the need for African American donors. A donor who decides to be an "African American Hero" takes a tie tag and hands it to the phlebotomist. Once the donor meets all of the usual donor criteria, the collection staff attaches the blue tie tag to the primary collection bag. The tie tag remains with the unit while other components are made from the donation. Plasma and platelets are not labeled with a tie tag. The tie tag is the marker to ensure that each RBC is captured as a CSCDP unit. The RBCs are placed in storage locations according to the C, E, and K phenotype of the component, thus making the units easily accessible when the order for transfusion is being completed.

Since the donors are very likely to be African Americans, extended typing for antigens in the Kidd, Duffy, and MNS systems are not performed, as the population frequencies of these antigens are similar in the donors and patients. However, segments are retained for testing for rare blood types. African Americans are the population of interest for antigens such as hr^B, U, Js^b, and Hy, as this population has the highest chance (albeit low) to be negative for these

antigens. If a rare blood type is found, the unit is selected for long-term storage in the frozen state and the donor is invited to be listed in the American Rare Donor Program.

Communication Process Between the Transfusion Service and Blood Supplier

Our transfusion protocol for patients with SCD requires some effort on the part of the blood bank technologist. Ideally, for each patient's blood order, units must be obtained from the blue tag inventory that are leukocyte-reduced, irradiated, less than 21 days old, ABO and D type-specific, crossmatch compatible, phenotype matched for C, E, and K, as well as antigen negative for other clinically significant antibodies present in the patient's plasma. This protocol is the same for all patients with SCD, whether they are inpatients or outpatients, scheduled or emergent, except that the freshness criterion is not applied for acute transfusions. The expectation for outpatient transfusions, which comprise the majority of these transfusions, is that patients will have their blood bank specimens drawn 1 to 3 days before the transfusion so as not to wait for blood availability when they arrive for the transfusions.

To meet these demands, there must be good coordination between the clinical service, the blood bank, the blood supplier, and the regional and national reference laboratories. Each week, the schedule of outpatient transfusions for the following week is compiled for both simple transfusions and RBC exchanges and is transmitted by fax to the blood bank. This schedule shows the anticipated date of transfusion and the anticipated number of units or volume of RBCs needed. A blood bank technologist reviews this schedule with the patient's ABO blood group, D type, C, E, and K phenotype, and antibody history, and then places a blood order with the ARC for each patient's needs, typically two days after the initial fax. The technologist will sometimes order 1 or 2 additional units if the patient has a history of clinically insignificant antibodies that interfere with cross-matching. In addition, the technologist will review the existing inventory of blue tag units and will order additional units to accommodate unscheduled blood orders for patients with SCD. This inventory of extra units typically consists of 5 group A and 5 group O, all negative for C, E, and K; this selection maximizes flexibility in using them for unscheduled needs. Finally, the technologist identifies blue tag units that are older than 21 days of storage, removes the blue tag, and transfers them to the general RBC inventory.

The ARC IRL must then find units to fill these orders, using units that will be less than 21 days old on the date of transfusion and selected from the blue tag inventory, if possible. Since the CSCDP provides a generous supply of RBCs from a predominantly African American background, the IRL is typically able to fill the majority of orders, amounting to 60 to 80 units each week, within 1 to 2 days. Orders for patients with complex antibody problems may take several more days. When the appropriate units are identified, they are shipped to the hospital blood bank where these units are stored separately from the rest of the available inventory.

Unique Features of the Program

Although this program is very successful in supporting our patients with SCD, there are some challenges when the patient does not exhibit one of the most common African American blood types. For example, for a patient who is e–, and develops an anti-e or autoanti-e, there may be difficulty in locating an e– blue tag RBC unit each time a transfusion is needed. Similarly, patients who form other antibodies, such as anti-S or -Jk^a, or -Jk^b, may not be able to be supported with blue tag units. If blood cannot be found in the blue tag inventory, the decision whether to delay transfusion or go outside the program must be made.

Blue tag units in our CSCDP are available for use for patients with elective and acute needs for blood transfusions to reduce the morbidity and mortality associated with SCD-related complications. Other programs that use directed or selected donations cannot often provide RBCs to patients with acute, nonelective needs for RBC transfusions. Our program continues to provide phenotype-matched RBCs for all patients with SCD and, when possible, attempts to transfuse patients using RBCs exclusively from this unique donor program.

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