Transfusion practices for patients with sickle cell disease at a major academic medical center

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The University of North Carolina at Chapel Hill (UNC) is a tertiary-care, academic university hospital and a major referral center for patients across the state of North Carolina. This 700-bed, Level 1 trauma center transfuses more than 22,000 RBC units to patients annually. Clinical services and areas of the hospital which rely most heavily on transfusion support for their activities are transplantation (bone marrow and solid organ), hematology, critical care (medical and surgical intensive care units), cardiothoracic surgery, pediatrics, the operating room, the emergency department, labor and delivery, dialysis, and outpatient services. UNC is recognized for its expertise in coagulation, transfusion medicine, and hematology, particularly in sickle cell disease (SCD). The sickle cell center at UNC, which began in 1980 and continues today, in conjunction with our neighboring institution, Duke University Medical Center, is designated as part of a National Institutes of Health comprehensive sickle cell center. Several of the physicians are dedicated to the care of pediatric and adult patients with SCD, as well as to research on transfusion management of these patients and recruitment of African American blood donors. This article describes the practices of this institution for transfusion management of patients with SCD, as well as some of its efforts related to this challenging area of transfusion medicine. ***Immunohematology* 2006;22:103–107.**

As a comprehensive sickle cell center (CSSC), the University of North Carolina at Chapel Hill (UNC) encounters patients of all ages with a variety of HbS hemoglobinopathies; the most commonly treated are patients with Hb SS, Hb SC, and Hb Sβ-thal.

On the basis of the CSSC 2005 census, there were 586 active patients with SCD, or approximately 50 per month, treated at our institution. Of these, 14 to 15 or approximately one-third were transfused each month. This frequency reflects the fact that many patients with SCD who have complex transfusion needs are ultimately referred to UNC for management.

Transfusion Therapy for Patients with SCD

Delivery of RBC transfusions to patients with SCD varies by method (simple vs. exchange) and frequency (episodic vs. chronic). In evaluating the need for simple versus exchange transfusion, a number of important factors should be considered. These include the acuity of anemia, the patient's baseline Hct prior to presenting for treatment, and the urgency of the need for oxygen-carrying capacity. Simple transfusions are often helpful as a first step to increase the oxygen-carrying capacity in a stable patient who presents with symptomatic anemia when such transfusions would increase the patient's Hct to a maximum of 33 percent.

The rheology of SCD is such that, above this threshold, complications from hyperviscosity may become a problem. When hyperviscosity or volume overload or both are a concern, or when a patient presents with life- or organ-threatening disease, exchange transfusion is the preferred method. Emergent automated exchanges are therefore performed for a variety of the indications in SCD, including stroke, acute chest syndrome, and hepatic sequestration. The goal of transfusion is to reduce HbS to 10 to 30 percent, depending on the clinical setting.

Also in place at UNC is a chronic RBC exchange program that has enrolled about 40 patients cumulatively since 1996 and currently has 20 active patients, the majority of whom are pediatric (65%). These patients are managed with apheresis RBC exchanges. Exchange transfusions and iron chelation therapy are the only two methods known to prevent iron overload patients receiving chronic transfusion therapy.[1] At our institution, pediatric patients with abnormal transcranial Doppler studies who are at risk for stroke and those with a history of stroke receive exchange transfusion in accordance with the STOP trials.[2,3] These patients will potentially receive life-long RBC exchange transfusions as new data indicate that their risk of stroke reverts back to baseline if transfusion therapy is stopped.[4] We are also part of the multi-institutional, ongoing clinical trial that uses exchange transfusion for pediatric patients with SCD and silent infarcts (silent infarct and transfusion trial: SIT). Although the use of

chronic transfusion therapy in adults after stroke has not been systematically studied, we perform RBC exchanges prophylactically in this setting. Other uses of chronic RBC exchange in our population include recurrent priapism and pulmonary hypertension in adults.

Other circumstances in which transfusion therapy is used include preoperative management of patients and pregnancy. In the former case, manual exchange is performed by the phlebotomy of 1 unit of RBCs followed by the simple transfusion of 1 to 2 units of RBCs to achieve a Hct of 33 percent. In the latter, transfusions are only used when a pregnancy is at risk because of SCD complications, with goals similar to those for a nonpregnant patient. We typically do not perform transfusions for patients with SCD who have controversial indications, such as recurrent nonhealing leg ulcers and debilitating pain, and before the use of IV contrast media.[5]

Transfusion Protocol

Because of the expertise of our health care providers and the frequency with which patients with SCD are transfused at our facility, the overall environment is favorable for reliable communication and consistent transfusion practice for these patients. Familiarity with the special requirements and transfusion complications in this patient population makes clear the need for appropriate identification of these patients before transfusion.

The blood component order form is an important tool that allows a physician to indicate the diagnosis of SCD and request special transfusion needs. Verbal communication of patient diagnosis or component attributes may also occur. This information is crucial for encounters with new patients without a prior history at our institution or blood bank. The blood bank history review, which occurs before patient testing, will also identify samples from patients with SCD in the laboratory. Some patients are recognized by name by virtue of the frequency of their visits or the complexity of their serologic testing.

Patient testing

Routine serologic testing on samples from patients with SCD is the same as that for any potential transfusion recipient; this testing includes ABO and D typing and antibody detection and identification, if necessary. Typing of the RBCs of these patients for C, E, c, e, K, Fy^a, Fy^b, M, N, S, s, P1, Le^a, and Le^b antigens is routinely performed when they are initially seen at our facility. Records from a referring facility may be helpful in instances where phenotyping is not possible or if transfusion of RBCs is urgently needed. If RBC transfusion has occurred recently, a hypotonic saline washing procedure can be performed to lyse allogeneic RBCs containing HbA to allow phenotyping of autologous RBCs.

Selection of RBC units for transfusion

All units of RBCs are prestorage leukocyte-reduced and ABO and D compatible with the patient's blood type. As inventory allows, units are selected that have been stored 14 days or less. Pretransfusion prophylactic phenotype matching is routinely and consistently performed for C, E, and K. If other clinically significant antibodies are present in the patient's plasma, or are historically known, appropriate antigen-negative RBCs are selected in addition to those typed as C–, E–, and K–. HbS testing of RBCs (Sickle Dex, Ortho-Clinical Diagnostics, Raritan, NJ) is performed when requested by the clinician or automatically for apheresis RBC exchange procedures. To calculate accurate RBC replacement volumes for these exchanges, quantitative Hb electrophoresis is performed.

Rationale

The rationale for pretransfusion prophylactic phenotype matching for C, E, and K is related to the immunogenicity of these antigens. The overall alloimmunization rate for chronically transfused patients with SCD is much higher than that for other similarly transfused populations, estimated at 25 to 30 percent.[6–9] While the majority of these patients will not form antibodies, those that do may experience complications including hemolytic transfusion reactions, stimulation of sickle cell crises, and increased difficulty of finding compatible RBCs when needed in the future. A general cautious approach at our institution has been shaped by the clinical experience of managing more severe transfusion complications in patients with SCD, such as hyperhemolysis. Because it is relatively easy to select C–, E–, and K– units from our general inventory, we can effectively prevent alloimmunization to these most immunogenic antigens.[6–9] Although alloimmunization rates of these patients at our institution have not been specifically measured, the occurrence of new antibodies is infrequent and certainly less than 25 percent for those patients transfused exclusively at our facility. However, newly

identified antibodies directed against low-incidence antigens, such as Js^a, and warm autoantibodies do occur. On occasion, patients are transfused elsewhere without partial phenotype matching and then transferred to our facility. In this setting, we have seen sensitization to Rh and Kell antigens and, less commonly, delayed transfusion reactions because of anti-S, anti-Jk^a, and anti-Jk^b. Sensitization to the latter antigens is also a possibility at our facility because we do not routinely provide RBCs negative for these antigens unless the plasma had a broadly reactive warm autoantibody or there was a previously identified alloantibody.

Special considerations

Extended phenotype matching is performed whenever possible in patients with SCD with warm autoantibodies, especially when the autoantibody is causing hemolysis. If the warm-reactive autoagglutinin is not associated with hemolysis, phenotype matching of RBCs is limited to C, E, and K and those indicated by antibody identification. Units for transfusion are selected on the basis of compatibility tests showing reactivity no stronger than those with the autologous RBCs.

For patients with antibodies to low-incidence antigens, RBCs for transfusion are selected on the basis of their compatibility by the IAT. If the antibody is no longer detectable and has an identified specificity, antigen-negative RBCs are requested from our blood supplier in advance. If appropriate antisera are not available to type units, RBCs are accepted from donors on the basis of historic antigen typing. If there is insufficient time for these pretransfusion steps, the ordering physician signs a conditional release card that provides documentation of his recognition of a possible, albeit unlikely, anamnestic immune response if the patient is re-exposed to the low-incidence antigen. This ensures that a proper risk and benefit assessment is made and also provides the opportunity for the blood bank physician to communicate with and educate the ordering physicians.

Our interest in blood bank practices for patients with SCD prompted systematic inquiry at the state and national level. We conducted a cross-sectional survey of North Carolina hospitals with blood bank facilities to assess hospital and patient demographics, as well as the services, testing, and blood components offered to patients with SCD.[10] Data from 76 of 106 (70%) hospitals showed the majority to be community hospitals (90%) whose blood banks saw a wide range of patients with SCD each month (0 to 30; median = 1). While all provided simple transfusion services, only 16 percent performed exchange transfusions, and 7 percent provided chronic transfusion programs. Less than one-third (29%) of these hospital blood banks had specific policies or procedures for patients with SCD. Less than one-half routinely provided HbS-negative RBCs (42%). With respect to the use of phenotype-matched RBCs, 38 percent provided antigen-matched RBCs, but only one-half (17%) did this prophylactically. Those providing phenotype-matched RBCs were more likely ($p < 0.001$) to have a trauma center (84% vs. 25%), to have policies for work-ups for patients with SCD (77% vs. 19%), to perform routine RBC phenotyping (50% vs. 4%), and to provide HbS-negative RBCs (65% vs. 16%).

We also conducted a national survey of major academic medical centers to ascertain current practices in selecting RBCs for the transfusion of patients with SCD.[11] Thirty-seven of 50 (74%) centers responded. The majority did perform partial phenotype matching of RBCs; however, a specific standard of care was not apparent. The most common antigens matched prophylactically were: E (73%), K (70%), and C (68%), followed by c (41%), and e (41%). There were also differences in transfusion practices for pediatric versus adult patients with SCD. Because of our experience, published data, and the results of these surveys, we continue to advocate the standardization of SCD transfusion practice to guide health care providers at both major academic medical centers as well as community-based hospitals.

Blood Supply Issues

Providing blood to this population can be challenging. Although the majority of patients do not form antibodies, those that do can present a problem in finding compatible RBCs. As a group, patients with SCD are the largest users of the national rare blood inventory, using up to one-third of the rare blood supply.[12] Therefore, excellent communication between our hospital transfusion service and our regional blood supplier is essential.

To fill that need, we have developed several strategies with our blood supplier. These include on-demand 24-hour access to units with special attributes for emergent indications and the ability to discuss special needs with either a reference laboratory specialist or the blood supplier's medical director.

RBCs for scheduled automated exchanges are ordered in advance and arrive in time for HbS testing and crossmatching at our facility. Our blood supplier provides reliable and safe blood resources and, with the added service of an advanced reference laboratory, even our most complex transfusion recipients can be managed appropriately. Nonetheless, the need for more active recruitment of donors within the African American community still exists.

A few centers that specialize in treating patients with SCD in conjunction with their regional blood collection facilities have begun programs to actively recruit and retain African American donors for their patients with SCD. These programs have mostly focused on matching these donors with the transfusion needs of their pediatric population. African American donors are asked to donate up to four times a year for the patients with SCD with whom they are matched. The degree of matching varies. Most of these centers provide C-, E-, and K-matched RBCs for these patients and have a readily available inventory in which to find rare RBCs. Others have attempted to provide extended, phenotypically matched RBCs for all of the transfusion needs of these patients. These types of programs require extensive commitment on the part of the blood center to coordinate donor collections with patient transfusion needs; staffing, donor recruitment, and donor retention are critical. The success of such programs in improving transfusion care to patients with SCD appears anecdotally to be good, decreasing alloimmunization rates in the short term. However, long-term effects have not been studied.

In our region, no specific donor recruitment process exists except on a local level. One of our institutional goals is to develop an active recruitment and retention program to match African American donors and patients with SCD, focusing our recruitment on donors at the 11 historically black colleges and universities (HBCUs) in our state. The HBCUs are a potentially rich source of African American donors that to date have been underused. Currently, one such program at a local HBCU has been widely successful in recruiting and retaining African American donors and has been cited by the American Red Cross as "a model for colleges and universities nationwide."[13] Active research is ongoing with this institution in an attempt to learn and understand the key components that have made it successful, and to adopt these components into a workable program that can be used at other institutions in our state.[14]

Conclusions

Patients with SCD provide many challenges for the field of blood banking and transfusion medicine. Our institution has taken a number of steps to ensure that practices here are consistent with national recommendations. We are fortunate to have a reliable blood supplier to facilitate the standard of care adopted at this center and we are pleased with the strides to examine SCD transfusion practices at the local, state, and national levels. There remains a need to standardize practices to minimize morbidity associated with transfusion in this population. Efforts need to be directed at academic medical centers, but must also reach community-based hospitals where many of these patients present during crises. Accomplishing this goal will ultimately require consensus within the blood banking community and recruitment of donors who can best meet the RBC phenotype needs of these patients.

References

1. National Institutes of Health, National Heart, Lung, and Blood Institute. Management of sickle cell disease. 4th ed. Washington, DC: National Institutes of Health; 2002. NIH publication 02-2117. http://www.nhlbi.nih.gov/health/prof/blood/sickle/sc_mngt.pdf.
2. Adams, RJ, McKie VC, Carl EM, et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. Ann of Neurol 1997;42:699-704.
3. Adams, RJ, McKie VC, Hsu L, et al. Prevention of first stroke by transfusion in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998; 339:5-11.
4. Adams RJ, Brambilla D; for the optimizing primary stroke prevention in sickle cell anemia (STOP 2) trial investigators. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med 2005; 353:2769-78.
5. Ohene-Frempong K. Indications for red cell transfusion in sickle cell disease. Semin in Hematol 2001;38(Suppl 1):5-13.
6. Vichinsky EP, Earles A, Johnson RA, Hoag MS, Williams A, Lubin B. Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. N Engl J Med 1990;322:1617-21.

7. Rosse WF, Gallagher D, Kinney TR, et al. Transfusion and alloimmunization in sickle cell disease. Blood 1990;76:1431-7.
8. Orlina A, Sosler SD, Koshy M. Problems of chronic transfusion in sickle cell disease. J Clin Apher 1991;6:234-240.
9. Ambruso DR, Githens JH, Alcorn R, et al. Experience with donors matched for minor blood group antigens in patients with sickle cell anemia who are receiving chronic transfusion therapy. Transfusion 1987;27:94-8.
10. Afenyi-Annan A, Lottenberg R, Konrad TR. Blood bank practices for sickle cell patients in North Carolina (abstract). Transfusion 2004;44(Suppl 9):135.
11. Afenyi-Annan A, Brecher M. Pre-transfusion phenotype matching for sickle cell patients (letter). Transfusion 2004;44:619-20.
12. Mallory D, Malamut D, Sandler SG. A decade of rare donor services in the United States. Vox Sang 1992;63:186-91.
13. American Red Cross."CIAA Increase Minority Blood and Bone Marrow Donations." Available at: http://www.redcross.org/article/0,1072,0_332_2317,00.html. Accessed March 5, 2004.
14. Afenyi-Annan A, Parrish T. African American blood donors at a local historically black college/ university (abstract). Transfusion 2004;44(Suppl 9):183-18.

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