Children’s National Medical Center’s transfusion protocol for sickle hemoglobinopathies

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Children’s National Medical Center (CNMC) is located in the nation’s capital of Washington, DC; this area has a large international population because of its embassies and chanceries; the World Bank, and other government and international agencies; and the presence of Howard University and its graduate schools with a large international student body. As of July 2006, CNMC has a roster of 1058 patients, aged 0 to 21 years, with sickle cell disease (SCD) or another hemoglobin S (HbS) hemoglobinopathy. Patients are followed in one of several SCD clinics, which include several specialized treatment sites with programmatic emphasis on the newborn infant, hydroxyurea treatment, chronic pain, pulmonary disease, sleep apnea, and pulmonary hypertension. Through our participation in a number of National Heart Lung and Blood Institute (NHLBI)-funded clinical trials, Stroke Prevention in Sickle Cell Anemia (STOP II), Stroke with Transfusions Changing to Hydroxyurea (SWiTCH), Silent Cerebral Infarct Trial and Hydroxyurea Trials (SITT), special sessions for the education of parents and children, and screening of potentially eligible patients for stroke prevention have also been developed. We currently treat 47 patients with chronic transfusion protocols. Our 26-bed hematology oncology unit has an average inpatient census of 8 to 10 patients with SCD. In fiscal year (FY) 2005, there were 530 inpatient hospitalizations and 3300 outpatient visits. Among inpatients, approxi-mately 40 percent were transfused for complications related to acute chest syndrome, acute splenic sequestration, or acute stroke, or in preparation for a surgical procedure, most often cholecystectomy.

CNMC developed its own blood donor center (BDC) in 1992, initially in concert with the American Red Cross, but it is now free-standing and independent. Blood components are provided to our patients exclusively from these two sources. In FY 2006, CNMC drew 2389 and transfused 1797 units of RBCs to 2536 patients, a portion of whom were patients with SCD or other hemoglobinopathies. An active therapeutic apheresis, and donor platelet and plasma donor pheresis, program is integral to the BDC. In FY 2006, 51 therapeutic erythrocytapheresis procedures were performed for acute complications of SCD or for patients on chronic transfusion regimens. Limitations on staffing, space, and equipment, and an increase in blood component requirements, along with competition for hematopoietic stem cell (HSC) collections preclude a greater therapeutic apheresis program for patients with SCD at the present time.

SCD Transfusion Protocol

Since 1976, under the supervision of one of the authors (Luban), the CNMC Blood Bank has followed the same protocol. All new patients are identified weekly by the patient care team and a full RBC phenotype is completed during the patient’s first hospitalization. This information is recorded in the laboratory information system (now computerized) along with a restriction for HbS negative RBCs. Three modes of transfusion are currently used. These include simple transfusion for acute symptomatic anemia exacerbation and in preparation for a surgical procedure, partial exchange transfusion, and erythrocytapheresis. Among the 47 patients on chronic transfusion regimen, 6 are on partial exchange transfusion as required by specific protocol, 6 are on erythrocytapheresis, and 35 are on simple transfusion. The goal for patients on chronic transfusion is to ensure a quantitative HbS concentration of less than 30 percent as measured by a pretransfusion quantitative HbS. The patient’s Hb and Hct are used to determine the volume of RBCs to be used at each transfusion. Additive anticoagulant RBCs are used unless the child is in florid renal or hepatic failure.
Phenotype matching is performed for patients on protocols when such matching is required. Patients not on research protocols do not receive phenotypically matched RBCs until they develop their first clinically significant antibody (-Le\textsuperscript{a}, -Le\textsuperscript{b}, and -M excluded). After development of their first antibody, they receive units phenotypically matched for C, E, and K. After the development of a second clinically significant antibody, they receive fully phenotypically matched units.

CNMC began bedside leukocyte-reduction of RBCs in 1988 and has had a fully prestorage leukocyte-reduced RBC supply since 1998. All patients, regardless of diagnosis, receive leukocyte-reduced RBC components. CMV seronegative units are reserved for those children who are to undergo HSC transplant; they are placed on this additional restriction after ensuring the CMV seronegativity status of their serum and that of the donors during the pretransplant evaluation. Irradiation restrictions for children with SCD are applied once the patient is listed for HSC transplant.

Our protocol of exchange transfusion with erythrocytapheresis is a modification of the aforementioned protocol. When an emergency erythrocytapheresis is indicated and time permits, RBCs phenotypically matched for C, E, and K are selected. The decision to forego phenotype matching is made by the blood bank director, who is also a practicing pediatric hematologist, and the medical supervisor of apheresis. Decisions are based on the clinical condition of the patient’s cardiorespiratory status, neurological 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, and incorporates principles of physics. 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 (5–7 days old) are used toward the end of the procedure as this represents the major (70%) fraction of RBCs remaining in the patient. These concepts are detailed by mathematical formula.\textsuperscript{1}

We have established clinical pathways for acute chest syndrome (ACS), stroke, fever, pain, and presurgical preparation, some of which include transfusion. For example, our ACS pathway includes a simple transfusion in children with an infiltrate on chest x-ray, an O\textsubscript{2} requirement, and an arterial blood gas with pO\textsubscript{2} less than 70 percent. This early intervention, coupled with aggressive pulmonary toilet, has significantly reduced the number of exchange transfusions for ACS and PICU admissions. The stroke pathway involves input from representatives of neurology, neuroradiology, cardiology, ICU, hematology, transfusion medicine, and laboratory medicine who are alerted when a new patient presents with an acute neurologic event. Erythrocytapheresis is performed as soon as logistically possible and within 12 hours of presentation to CNMC emergency department.

**CNMC “Buddy” Program**

Our desire to exclusively use leukocyte-reduced RBC components, and the recognition that donors with sickle cell trait could not provide RBCs for prestorage leukocyte-reduction because of filter failures,\textsuperscript{4} prompted the change in the direction of our Buddy Program. Initiated in 1998 and expanded in 2002, our program was established to increase the number of African American donors who were phenotyped and committed to frequent donations for our patients. We contact all parents of 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. Blood samples from donors are initially tested for HbS and other hemoglobinopathies; if found to be of the AA hemoglobin phenotype, their RBCs are fully antigen-typed and their demographic, contact, blood group, and RBC phenotype are entered into a computer program shared with the BDC. 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 the blood supplier. There are only 6 children whose complex allo- and autoantibody status precludes us from finding donors except through the rare donor registry of our blood supplier. These intermittently transfused patients include one with an anti-C, -E, -N, -V, -Fy\textsuperscript{a}, -Js\textsuperscript{a}, cold and warm autoantibody and another with anti-C, -K, -V, -Js\textsuperscript{a}, and -Go\textsuperscript{a}. For these and selected other cases, the transfusion service places the orders with the blood supplier. In 2006, the Buddy Program supplied all or part of the transfusion needs of 53 patients. With
the establishment of a blood mobile in the first quarter of this fiscal year, focused donor recruitment and collection efforts should enable provision of more units for each patient.

Ensuring Communication Concerning Allo- and Autoantibody Formation

Of 190 children transfused more than twice, 51, or 27 percent, have clinically significant antibodies. These include 5 with only autoantibodies and 46 with alloantibodies, of whom 9 also have autoantibodies. None have been pregnant. This rate of antibody formation is similar to what has been previously reported.6,7,8 As soon as an alloantibody, additional alloantibody, or autoantibody is identified, a series of events occur. These include sending a letter to the parents 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 (MediAlert bracelet, MediAlert Foundation, Turlock, CA); updating information in the electronic medical record; placing restrictions in the computerized laboratory information system with paper card file backup; and providing a copy of the patient letter to the patient convenience chart and patient care team.

While most children with SCD and other hemoglobinopathies in the DC metropolitan area are cared for at CNMC, international and regional travel, including summer camp experiences, can put children with antibodies at risk should they need transfusions. Our solution is to encourage wearing an identification bracelet (MediAlert bracelet, MediAlert Foundation) or similar national system with instant access to this critical information. When teenagers from CNMC make the transition to adult care, their allo- and autoantibody information is included as part of the detailed transitional medical history. Detailed letters with full phenotype and antibody history are prepared for families returning to their home country or on travel.

Rationale for the CNMC Phenotype Matching Policy

CNMC participated in the Cooperative Study of Sickle Cell Disease (CSSCD), one of the very first multi-institutional NHLBI-sponsored data collection and intervention studies. While contributing to the CSSCD study design, it became obvious that CNMC had a larger number of non-American born children with HbS hemoglobinopathies and that these children tended to have a greater number of antibodies per child and more unusual antibodies, and occasionally became non-transfusible unless blood was obtained through the rare donor registry. This prompted a CNMC-published study on differences in alloantibody development, and served as the basis of studies by others that attempted to identify the pathophysiology of antibody development, looking at HLA and the impact of phenotype matching on antibody development.7-11 CSSCD demonstrated an alloimmunization rate of 18.6 percent and noted that the chances of sensitization continue to rise with increasing number of transfusions.6 Based on our experience and clinical expertise, it is thought that the CNMC protocol ensures rapid availability of RBCs when needed for acute complications of SCD, and for acute erythrocytapheresis, while overburdening neither the blood supplier nor the CNMC BDC or transfusion service. The protocol also protects the chronically transfused children whose risk may increase with subsequent transfusion through use of phenotypically matched RBCs from a donor pool more racially matched to the child.

Unanswered Questions

The advantages of initiating complete phenotype matching at inception of first transfusion have never been demonstrated. Whether there is genetic predisposition to allo- and autoantibody formation is also unanswered.12 The reason that certain RBC antigens are more likely to elicit sensitization is also unknown although antigen density and other factors have been implicated. No criteria backed with pathophysiological measures have been established regarding the timing of acute erythrocytapheresis for patients with frank ischemic stroke, transient ischemic attacks, or incipient or frank ACS. While erythrocytapheresis with or without hemodilution but with aggressive chelation can decrease the transfusional iron burden, the timing, cost, and effect of the increase in blood donor exposure and the risk of catheter placement must be kept in mind when suggesting these modalities as standard of care. Future clinical and translational studies detailing the pathophysiologic mechanisms of allo- and autosensitization are needed.
References


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