EDUCATIONAL COMMENTARY – RBC TRANSFUSIONS IN PATIENTS WITH SICKLE CELL DISEASE

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Learning Outcomes

On completion of this exercise, the participant should be able to

- understand the pathophysiology of sickle cell disease;
- assess indications for red blood cell (RBC) transfusions in patients with sickle cell disease;
- recognize the importance of providing phenotypically matched RBCs in this patient population;
  and
- understand the methods used to provide antigen-negative blood.

Case Study

A 7-year old girl was practicing her ballet routine for an upcoming dance recital and experienced shortness of breath; bilateral leg, chest, and abdominal pain; and fatigue. She was brought to the emergency department. On arrival, her temperature was 39°C; pulse, 130 beats/min; respiratory rate, 44/min; and blood pressure, 140/88 mmHg. Her hemoglobin concentration was 7.7 g/dL. Her family history was positive for sickle cell trait. A peripheral blood smear showed sickled cells (Figure).

![Peripheral Smear](http://accessmedicine.mhmedical.com/data/books/1900/m_pathblood2_ch9_f001.png)
Hemoglobin electrophoresis was performed during her hospital admission. Her results were >90% hemoglobin S (HbS), <10% HbF, and <3.5% HbA2. Based on the electrophoretic pattern, she was diagnosed as having sickle cell disease, genotype SS.

Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive disorder. It is caused by the substitution of valine for glutamic acid at the 6th position of the hemoglobin β chain, which results in the abnormal sickling pattern of the hemoglobin. The sickling is caused when the abnormal hemoglobin polymerizes during periods of decreased oxygenation in the body, such as exercise and high altitude. The red blood cells (RBCs) become rigid and deformed. They occlude the microvasculature and cause tissue hypoxia and infarction. The life span of RBCs in persons with sickle cell disease is short, less than 20 days in the circulation (normal life span of RBCs is ~120 days).

The disease affects approximately 100,000 individuals in the United States. Approximately 1 in 365 African-American children and 1 in 16,300 Hispanic-American children are born with SCD. In addition, SCD can be found in persons whose ancestry is from Saudi Arabia, India, and Mediterranean countries. The life expectancy of persons with SCD was short through the 1960s; few lived until their 20s. However, together with vaccination, prophylactic penicillin, and the development of hydroxyurea, the utilization of blood transfusions to manage SCD has dramatically increased life expectancy, with most people with SCD surviving into their 60s.

Blood Transfusions

Red blood cell transfusions are the cornerstone of SCD management. In addition to preoperative management, transfusion is used to treat and prevent many acute and chronic manifestations of the disease, including silent cerebral infarcts, acute chest syndrome, and splenic sequestration. It is associated with dramatic reductions in morbidity and mortality.

The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study showed that preoperative transfusion in this population decreased perioperative complications. Patients with SCD who did not receive preoperative transfusions had more complications that those who were transfused.

Silent cerebral infarcts are commonly seen in patients with sickle cell disease, and the rate of recurrence is increased over that of the general population. In a randomized controlled trial in the pediatric SCD population that involved two groups, an observation group and a transfusion group, regular blood transfusions reduced the recurrence of cerebral infarcts. The Stroke Prevention (STOP) trials similarly
demonstrated the need for and efficacy of long-term regular transfusions for the prevention of primary strokes in patients with SCD.\textsuperscript{4}

Acute chest syndrome is defined as a new infiltrate present on a chest x-ray in a patient with SCD. The individual may also experience chest pain, tachypnea, wheezing, and cough. The STOP trial also showed that RBC transfusions improved outcomes in SCD patients with acute chest syndrome.

**Alloimmunization**

There are many risks involved in transfusions in the general population, including infectious disease transmission and transfusion reactions. In patients with SCD, there is also an increased concern for alloimmunization, given that these patients are chronically transfused. Currently, approximately 80% of patients with SCD have a history of transfusion.\textsuperscript{5} Alloimmunization is defined as the immune response to foreign antigens after exposure to genetically different cells or tissues. Patients with SCD are usually alloimmunized because they begin to receive transfusions starting at a young age and are transfused frequently. In the United States, in the SCD population who receive regular transfusions the alloimmunization rate is 58%, in comparison to the general population where only 10% of persons who receive transfusions are alloimmunized.\textsuperscript{6}

The potential reason for the increased sensitization is exposure to RBCs from blood donors of European descent. There are many polymorphic differences in the RBC antigens found in a European-descent donor and the recipient with SCD (who is often not of European descent). Alloimmunization rates range from 20% to 50% among transfusion recipients with SCD in the United States. In comparison, in a homogenously similar population of donors and recipients, the rate of alloimmunization among patients with SCD was 6.1% in Uganda and 2.6% in Jamaica. The rationale that racial antigenic differences result in increased alloimmunization rates was also supported by a study in Asian patients with thalassemia who received transfusions of RBCs from donors of European descent. These patients had increased alloimmunization rates in comparison to recipients who were of European descent.

The problems associated with alloimmunization are significant. Treatment of a patient with SCD could be delayed because of the difficulty of finding crossmatch-compatible RBCs for the transfusion or exchange. The patient may develop a delayed hemolytic transfusion reaction resulting in hyperhemolysis, the destruction of not only the transfused cells but also the patient’s own RBCs. This process can be life-threatening. The pathophysiology of hyperhemolysis is not fully understood, but the potential rationale is that alloimmunization may mediate autoantibody production.
In patients with SCD who are transfused and are alloimmunized, approximately 50% to 75% develop an antibody to the Rh system. According to a study conducted by Vichinsky, approximately 53% of patients developed multiple clinically significant antibodies. The most common Rh antibody formed is an anti-E. The other significant antibodies formed are anti-C, anti-K, anti-Jk(a), anti-Jk(b) and anti-Le. Given the frequency of antibody development, matching for Rh (C, c, E, e) and Kell antigens is the standard of care at many hospitals. It is preferable to provide RBCs that are ABO and Rh compatible and are negative for C, E, and K antigens.

A retrospective study that demonstrated the utility of antigen matching was conducted by Castro, et al during a 12-year period. This study reviewed and divided patients into 5 different protocols based on the extent of antigen matching that was performed in those transfusion recipients with SCD. The different protocols used are shown below:

- Protocol 1: Rh matched (C, c, E, e)
- Protocol 2: Rh (C, c, E, e) and Kell matched
- Protocol 3: Rh (C, c, E, e), Kell and S matched
- Protocol 4: Rh (C, c, E, e), Kell, S, and Fy(a) matched
- Protocol 5: Rh (C, c, E, e), Kell, S, Fy(a) and Jk(b) matched

The most efficacious protocol in preventing alloantibody formation was protocol #5. It prevented the formation of antibody in 71% of patients with SCD. The protocol commonly used at most institutions (#2) prevented antibody formation in 53% of the patients studied. The drawback of extended matching is that it may dramatically reduce the blood supply available to SCD patients. In comparison to protocol #5 where only 0.6% of European-descent blood donors would qualify, 14% of these blood donors would meet the criteria for protocol #2.

Another study on RBC matching in the SCD population was conducted by the Blood Center of Wisconsin. The researchers demonstrated that Rh and Kell matching reduced the rate of alloimmunization from 23% to less than 1.5%. In patients who received transfusions, only 1.3% became alloimmunized. Similarly, the University of Colorado employed an extended matching of antigens (Rh, Kell, Kidd, and Duffy). Among 99 patients with SCD who were transfused using this matching protocol, only seven developed antibodies.

**Strategies**

To determine the appropriate antigen-negative RBC units to provide to a patient with SCD, complete phenotyping is suggested the first time the patient presents to the hospital for blood transfusion. The phenotype can be performed through serologic or molecular methods. Although prospective
crossmatching can prevent alloimmunization, this strategy can be cost-prohibitive for many institutions, especially when using extended phenotyping. Therefore, some institutions provide antigen-matched blood only to those patients who have previously formed antibodies.

Transfusions with RBC units from donors of matching descent have also been proposed as a means to decrease alloimmunization rates among patients with SCD. A directed blood donor program was instituted by Charles R. Drew University. In this study, donors and recipients were paired according to ABO, Rh, and Kell status. No recipients in this directed program developed antibodies despite receiving multiple transfusions. Another such initiative was conducted by Children's Hospital Oakland. In this program, the patients received RBC units that were matched for Rh and Kell antigens when they developed an alloantibody. However, phenotyping of patients was done before the transfusions were initiated. Directed blood donor programs require that substantial resources be available to recruit and coordinate donors for individual patients and for the testing and provision of blood to patients with SCD.

Other proposed strategies for decreasing alloimmunization in these patients include judicious use of RBCs and providing leukocyte-reduced RBCs, thus limiting donor and immunogenic exposure in this group of patients.

Conclusions

Patients with sickle cell disease often receive transfusions because sickled cells in their circulation mediate many acute and chronic clinical manifestations of the disease, including acute chest syndrome and stroke. Red blood cell transfusions provide many therapeutic benefits in these patients. However, RBC alloimmunization is a challenge in this population, because it can lead to life-threatening events such as hyperhemolysis and the difficulty in finding compatible blood can delay treatment in these patients. Antigen matching and directed-donor programs are means by which institutions have tried to decrease alloimmunization rates among patients with SCD. The use of these techniques to manage SCD varies across institutions. The primary limiting factor is the prohibitive cost associated with phenotyping and matching donors and recipients.

References


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