Sickle cell disease: a review

S. D. Roseff

Sickle cell disease (SCD) is described as the first identified “molecular” disease since its manifestations stem from a substitution of valine for glutamic acid in the structure of the β-chain hemoglobin molecule. As a result of this change, RBCs form characteristic “sickle” shapes and the surface of these RBCs attract each other, polymerizing when in a low oxygen environment. This seemingly “small” variation in the structure of the RBC causing polymerization leads to manifestations such as chronic occlusion of blood vessels (vaso-occlusion), reduced blood flow to vital organs (ischemia), and alterations of the immune system. In addition, the abnormal sickle cells are prematurely removed from circulation, resulting in hemolytic anemia. Transfusion is a vital component of the treatment of some of the complications of SCD. It is also a modality used to prevent some of these complications from occurring. Patients with SCD are unique because those who are transfused usually require chronic transfusion, resulting in exposure to many different blood donors over the course of treatment. In addition, most patients with SCD in the United States are African American, and most donors are Caucasian from Western European descent. As a result of this difference, patients with SCD are exposed to RBC antigens that they lack, putting them at risk for forming alloantibodies, defined as RBC alloimmunization. Therefore, it is important to understand the issues involved in the safe and effective transfusion of patients with SCD.

Defining Hemoglobinopathies

Hemoglobin (Hgb) is made up of iron (heme) and 4 globin chains. The type of globin chains determines the type of hemoglobin (see Table 1). Since SCD is characterized by the presence of an abnormal or variant hemoglobin, hemoglobin S, it is characterized as a hemoglobinopathy. The composition of hemoglobin for patients with homozygous SS is presented in Table 2.

There are a variety of other abnormal hemoglobins that may be present with or without Hgb S. The type of hemoglobin a person has is based on patterns of inheritance. If each parent contributes hemoglobin S, the child can inherit two copies and is designated as Hgb SS, or is homozygous for hemoglobin S. If a child only inherits one copy from one parent and a copy of normal hemoglobin, Hgb A, they are designated as Hgb AS, or heterozygous. These individuals are usually asymptomatic, and only develop manifestations under rare circumstances, where they become hypoxic, such as at high altitudes. Therefore, not every person with an abnormal hemoglobin develops or exhibits signs and symptoms. Although Hgb S is found worldwide, it is most commonly found in western Africa. About one in every 400–500 African Americans, or 80,000, has SCD. About 9000 African Americans, or one in 12, have sickle cell trait.

On the other hand, patients who have manifestations of their sickle hemoglobin are considered to have SCD. This includes patients who are homozygous for Hgb SS, as described previously. In addition, some patients who inherit Hgb S from one parent and another abnormal hemoglobin from the other parent can also have SCD. Common examples are designated as Hgb SC and Sβ-thalassemia. These individuals can have a milder clinical course than that of individuals who are homozygous for Hgb S.

Since RBCs with Hgb S are abnormal, they are removed from circulation in the spleen more rapidly than normal RBCs. This leads to a reduced life in the circulation of 16–20 days in comparison to 120 days for normal RBCs. The premature destruction of RBCs, with the accompanying decrease in hemoglobin, is classified as a hemolytic anemia.

Table 1. Composition of normal adult hemoglobin

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Composition</th>
<th>Percent (%)</th>
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<tbody>
<tr>
<td>Hgb A</td>
<td>α2β2</td>
<td>96–98</td>
</tr>
<tr>
<td>Hgb A2</td>
<td>α2β2</td>
<td>1.5–3.5</td>
</tr>
<tr>
<td>Hgb F</td>
<td>α2γ2</td>
<td>&lt;1</td>
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Table 2. Hemoglobin SS (αβδ3)

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Percent (%)</th>
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<tbody>
<tr>
<td>Hgb S</td>
<td>80</td>
</tr>
<tr>
<td>Hgb A2</td>
<td>2–4.5</td>
</tr>
<tr>
<td>Hgb F</td>
<td>120</td>
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</table>

Typical Laboratory Findings in Sickle Cell Disease

Patients with SCD are commonly diagnosed after newborn screening. In the past, young children presented with painful swellings of the feet and hands, a consequence of vaso-occlusion (see discussion on Clinical Manifestations of Disease).

Many patients with SCD have anemia, with hemoglobin levels between 6 and 8 g/dL. Characteristic sickle shaped cells are seen on peripheral smear (Fig. 1). Patients do not always have symptomatic anemia because the body compensates for the peripheral RBC destruction by increasing the rate of RBC production (erythropoiesis) in the bone marrow. Consequently, the bone marrow contains an increase in the number of RBC precursors. As a result, immature RBCs, by an average of 80%.
precursors, suggestive of reticulocytes, are released from the marrow prematurely. Therefore, the peripheral smear will also show these immature RBCs, which are larger than mature RBCs and have a slightly blue color since they are not fully hemoglobinized. The term reticulocytes will be used in this education activity, and refers to these RBCs.

Another consequence of the high rate of hemolysis and erythropoiesis, or increased RBC turnover, is the accumulation of unconjugated or indirect bilirubin. As a result, some patients will have yellowing of the white of the eyes, scleral icterus, and skin, or jaundice. The increase in bilirubin also puts patients at increased risk for gallstones, and the patient may have to have their gallbladder removed. Table 3 lists the common laboratory findings in SCD and their etiologies.

Early diagnosis is essential in order to treat and even prevent some of the complications of SCD. In the past, approximately 25% of children between the ages of four months and five years with SCD died of pneumonia. The use of prophylactic penicillin in children with SCD in the past five years and five years with SCD died of pneumonia. The use of prophylactic penicillin in children with SCD in the past five years with SCD died of pneumonia.

<table>
<thead>
<tr>
<th>Laboratory value</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Low hemoglobin and hematocrit</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>High mean cellular volume (MCV)</td>
<td>Reticulocytes</td>
</tr>
<tr>
<td>High white blood cell (WBC) count</td>
<td>Inflammation and increased marrow production</td>
</tr>
<tr>
<td>High platelet count</td>
<td>Increased marrow production</td>
</tr>
<tr>
<td>High lactate dehydrogenase (LDH)</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>Low haptoglobin</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>High total and indirect bilirubin</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>High alkaline phosphatase until puberty</td>
<td>Elevated bone marrow activity</td>
</tr>
</tbody>
</table>

When performing patient testing, it is always important to follow the package insert and ensure that proficiency testing is performed in compliance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA). CLIA regulations require that laboratories enroll in a Centers for Medicare and Medicaid Services (CMS) approved proficiency testing (PT) program for all regulated tests that the laboratory performs.

Clinical Manifestations of Sickle Cell Disease

The function of a normal RBC is dependent upon its ability to flow freely through blood vessels and to be flexible enough to move in and out of vessels and tissue where oxygen delivery occurs. Due to the rigidity of the sickle RBC, these properties are lost. Interestingly, when a patient with SCD has a higher percentage of hemoglobin F, the course of their...
Hemoglobin and its interactions with blood vessels can lead to multiple complications in patients with sickle cell disease (SCD). The abnormal shape and surface of sickle cells result in their shortened life span in the circulation and lead to the characteristic anemia. As RBCs are cycled through the spleen, the site of their ultimate destruction, they also injure the tissue of the spleen. Their rigidity impairs their ability to flow smoothly through the sinusoids, and their sharp edges cause them to be stuck, and to damage splenic tissue. In children under the age of five, blood can pool in the spleen, which becomes a site of sequestration of RBCs. When this occurs, the child has a painful, enlarged spleen accompanied by a drop in hemoglobin. Splenic sequestration can be life-threatening since there is also a drop in blood volume in the vasculature, or hypovolemia. Transfusion management is essential in these cases. Many of these patients eventually need to have their spleen removed. As a patient gets older, the damage to the spleen is chronic, and the spleen actually becomes smaller, eventually shriveling and losing function.1,4,5

In order to keep up with this chronic destruction, the body attempts to compensate by increasing RBC production. This chronic hemolysis may also create an inflammatory state.1,10,11 Also, the free hemoglobin that is released
from hemolyzed RBCs causes additional damage to the lining of blood vessels. The marrow is very active, as evidenced by immature RBCs or reticulocytes in the peripheral blood. As the marrow increases production of RBCs, platelet and WBC production also increases. As a consequence of increased erythropoiesis, many patients do not suffer from signs and symptoms of anemia, even though they may have a low hemoglobin. As long as the individual can continue to compensate, the anemia does not present a problem. When the marrow cannot keep up with production (i.e., a lack of folic acid), or has its production impaired by viral illness, such as parvovirus B-19, an aplastic crisis may occur. Parvovirus B-19 is a common childhood virus responsible for Fifth’s Disease. This disease causes a rash, the classic “slapped-cheek” appearance, and high fevers. Parvovirus can suppress bone marrow production by destroying the RBC precursor cells in the bone marrow. In these cases of severe anemia, transfusion therapy is necessary.

**Immunologic and Infectious Manifestations**

The spleen can be affected in SCD due to occlusive forces, but it is also damaged by the pointed, inflexible sickle cells that travel through it and are stuck. The spleen is an important immunologic organ, helping to fight infections with encapsulated organisms (S. pneumoniae, H. influenzae, and N. meningitidis). Therefore, it is important to recognize children with SCD and immunize them. As stated earlier, the use of prophylactic penicillin has been found to reduce death in children. All infections should be treated aggressively.

**Treatment of Sickle Cell Disease**

Prevention of early complications, such as infection, is important in the overall treatment plan for patients with SCD. As more is being learned about the basic mechanisms of the disease, new treatments are being developed. Analgesics, including opioids, are a mainstay of treatment for people suffering with pain crisis. In addition, it is important to give patients with SCD vitamins, such as folic acid, which are essential to the production of RBCs. Hydration is also key, since RBCs sickle when dehydrated. In addition, hydration improves the viscosity of the patient’s blood and allows the RBCs to move more easily. As hemoglobin rises, the viscosity of the bloodstream increases and there is an increased risk of occlusive disorders, as well as an increased risk of pain crisis. There is no data to show that transfusion should be part of the routine treatment for crisis.

The role of nitric oxide is also being investigated as a therapeutic modality, since nitric oxide plays an important role in the physiology of RBCs.

Patients of all ages who have higher concentrations of Hgb F have milder disease and lower mortality than patients with lower levels of Hgb F. Increasing the production of Hgb F seems like a reasonable therapeutic intervention. In the laboratory, Hgb F has been shown to interfere with the polymerization of deoxygenated Hgb S. The chemotherapeutic agent, hydroxyurea (HU), increases the amount of Hgb F that is made by the bone marrow. RBCs with Hgb F lack the β chain, which is responsible for the sickling seen in Hgb S RBCs. Therefore, these RBCs do not sickle, nor can they polymerize. This is one of the mechanisms considered to be responsible for the improved outcomes. In addition, HU has been found to reduce WBC production, thereby reducing the number of circulating inflammatory cells, capable of adhering to blood vessel walls. Platelet counts also drop and this may inhibit one of the factors responsible for vaso-occlusion. HU also influences nitric oxide metabolism. Nitric oxide leads to the dilation of blood vessels and seems to reduce the adhesion between RBCs and blood vessel walls.

HU has been found to reduce mortality due to an induction of Hgb F and a reduction in vaso-occlusive events. In addition, it reduces the incidence of acute chest syndrome, transfusion requirements, episodes of hospitalization, pain crisis, and reduces blood flow through intracranial blood vessels, as measured by transcranial Doppler in children. Currently, there is controversy about whether or not HU can be used to prevent repeat strokes as effectively as chronic transfusion in children. Since HU is a chemotherapeutic agent, there is concern that it will have long term side effects. It is not used in women who are pregnant or planning to become pregnant. In addition, some patients have to discontinue therapy because their WBC count becomes too low. The effects of hydroxyurea are not immediate, generally taking a few months to be effective. Therefore, it does not provide rapid response during acute illness.

Bone marrow transplant, peripheral blood stem cell transplant, and umbilical cord blood transplant are all strategies that can cure SCD. Due to the morbidity and mortality secondary to transplant, it is important to carefully choose patients with severe disease with a high risk of morbidity and mortality, such as those with recurrent strokes. Therefore, trials have centered on treating children or young adults, and there are some encouraging results. Unfortunately, one impediment is the low availability of matched sibling donors.

**Transfusion Management**

Transfusion therapy should only be initiated in patients with signs and symptoms of anemia. As mentioned, most patients with SCD, though anemic, do not generally have daily signs and symptoms of anemia. Therefore, RBC transfusion should only be used for specific indications. RBC transfusion, when necessary in patients with SCD, provides some additional benefits. While increasing the patient’s hemoglobin, transfusion dilutes the Hgb S with Hgb A. The RBCs with Hgb A have longer survival than the RBCs with Hgb S and neither sickle nor polymerize. In addition, transfusion will suppress the patient’s own erythropoiesis, or RBC production. As a consequence, they will produce less of their own Hgb S RBCs.
Risks

RBCs can be transfused as a simple transfusion or via exchange transfusion (erythrocytopheresis). During simple transfusion, one or two units of RBCs are transfused through a peripheral IV. Exchange transfusion is usually performed using an automated machine that is designed to remove whole blood from the patient, separate into its various components, and then discard the patient’s Hgb S RBCs. RBCs from the blood bank are then used as replacement. Typically, an RBC exchange exchanges one to two RBC volumes (total blood volume × hematocrit = 1 blood volume). A larger bore, stiff-walled central venous catheter is usually required due to the flow requirements of the automated instrument. In the absence of automated equipment, manual exchange transfusion can be done. This is not optimal, since this can create blood pressure and volume changes during the alternating removal of whole blood through a peripheral vein with subsequent reinfusion of banked RBCs. Each type of transfusion has its own risks and benefits, as outlined in Table 4 and in Table 5.

Table 4. The benefits and risks of simple transfusion

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
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<tbody>
<tr>
<td>Technical ease—requires only peripheral IV access</td>
<td>Increases viscosity Risk of iron overload</td>
</tr>
<tr>
<td>Low donor exposure—only 1 or 2 units of RBCs necessary</td>
<td>Dilution of Hgb S</td>
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</table>

Table 5. The benefits and risks of exchange transfusion

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produces rapid reduction in Hgb S</td>
<td>Requires large gauge IV, usually central venous catheter</td>
</tr>
<tr>
<td>No increase in viscosity</td>
<td>Requires expertise and special equipment—may require transfer of patient to another facility</td>
</tr>
<tr>
<td>No risk of iron overload—some observe reductions in serum ferritin over time</td>
<td>Higher donor exposure—at least 4 units of RBCs for an adult, usually more</td>
</tr>
<tr>
<td></td>
<td>Higher expense</td>
</tr>
</tbody>
</table>

Indications for Transfusion in Sickle Cell Disease

Indications for transfusion in SCD include:

Aplastic Crisis: When RBC production in the bone marrow is interrupted, the delicate balance to maintain RBC production during chronic hemolysis is disrupted. Therefore, if the patient has a drop in their hemoglobin and becomes symptomatic, transfusion is required until the underlying process abates.

Splenic Sequestration: When a child’s hemoglobin drops and they become symptomatic, transfusion is necessary, in this setting. Of interest, transfusion increases the hemoglobin beyond what’s expected, so it is important to transfuse slowly to avoid over-transfusion. Hepatic sequestration can also occur.

Pregnancy: In uncomplicated pregnancies, there is no improvement in outcomes in women who are transfused. Patients with other complications of SCD should be transfused accordingly.

Presurgical Prophylaxis: Patients with SCD are at high risk for complications when undergoing major surgery. Currently, some practitioners recommend that patients be transfused to a hemoglobin of 10 g/dL prior to surgery. A study done comparing exchange transfusion to simple transfusion found that exchange transfusion is unnecessary. There are investigations underway to determine whether or not a hemoglobin lower than 10 g/dL is safe for certain surgeries.

Acute Chest Syndrome (ACS): Transfusion, either simple or exchange, implemented early in the course, improves oxygenation and alleviates organ dysfunction. For patients who are stable, simple transfusion should be performed. If the patient deteriorates, does not improve, or has a rapidly evolving course, exchange transfusion is recommended. Simple transfusion should only be performed until the hemoglobin reaches about 10 g/dL. Beyond that, there is concern for vaso-occlusion.

Stroke: Due to the ease of simple transfusion in pediatric patients, they usually undergo simple transfusion. For patients who have an initial stroke, exchange transfusion is used to rapidly reduce the amount of Hgb S that can be recruited and extend the immediate damage to the brain. Once a patient has a stroke, they are at risk for additional strokes. By performing a monthly transfusion, either simple or exchange, this risk of recurrence is reduced. A recent study showed that stopping monthly transfusion after the return of normal flow by transcranial Doppler results in recurrent strokes and the return of abnormal TCDs. Of interest, during studies to reduce the risk of first stroke, patients on a chronic transfusion protocol also had a reduction in the risk of acute chest syndrome and a reduction in the number of pain crises.
Adverse Consequences of Transfusion of Patients with Sickle Cell Disease

Adverse consequences of transfusion of patients with SCD include:

Alloimmunization: Due to the disparity between donors and patients with SCD in the United States, patients with SCD are among those most frequently alloimmunized. Studies have shown that the most common antibodies formed in this population are C, E, and K1. There are also other antibodies that are formed due to donor-recipient disparity. Therefore, in order to prevent alloimmunization, some centers routinely perform RBC phenotypes on patients with SCD and only transfuse RBCs that lack C, E, and K1, if the patient is negative for the antigen. This strategy reduces the rate of antibody formation in these at-risk patients. Despite these findings, practice is variable. Analyzing the results of the 2003 J-C College of American Pathologists Proficiency Testing Survey, Osby and Shulman found that only 37 percent of North American hospitals routinely perform antigen typing on the RBCs of non-alloimmunized patients with SCD. In the 439 laboratories that do perform RBC phenotyping, C, E, and K1 were the most frequent antigens that were matched. In a survey of 50 academic medical centers in the US and Canada, 73 percent of centers reported that they performed routine phenotyping with 89 percent of those centers also matching for C, E, and K1. There is controversy about providing RBCs that lack additional antigens. As you match for additional antigens, it becomes more difficult to find compatible units. It is argued that it is a better use of resources to save those rare units for patients with existing antibodies. Another strategy has been to use RBCs from donors who are ethnically similar to the patient, thereby creating a better chance that the donor and patient will match more closely. Whenever a patient develops an antibody, they will also receive RBCs lacking the corresponding antigen.

Hyperhemolytic Syndrome: A serious type of hemolytic transfusion reaction, called the "hyperhemolytic syndrome," can occur in the setting of transfusion. During these episodes, the patients are typically being transfused, and instead of rising, their hemoglobin falls with subsequent transfusion. It is felt that there is a "bystander" hemolysis of the patient's own RBCs, as well as destruction of transfused RBCs. Of interest, the units transfused are crossmatch compatible, and no new alloantibodies are identified at the time of transfusion. Further transfusion compounds the problem. Therefore, it is important to recognize the syndrome and, if possible, stop transfusing. If transfusion is necessary, intravenous immunoglobulin (IVIG) and intravenous steroids have been found to be effective. If transfusion is required because of life-threatening anemia, it should be done cautiously, using IVIG and steroids concurrently.

Iron Overload: Each unit of transfused RBCs contains about 200–250 mg of iron. With chronic transfusion, this iron accumulates and can be deposited into organs such as the heart, liver, and endocrine glands. In order to prevent this, medications are used to remove, or chelate, iron. Intravenous chelators have been used, but their efficacy is hindered by its half-life and poor patient compliance. A new generation of oral chelators is effective since there is increased compliance, and mode of actions results in a more continuous chelation. Serum ferritin is monitored in patients on chronic transfusion protocols who have SCD. The aim of treatment is to reduce serum ferritin and to remove iron from organs.

Transfusion Recommendations

When a patient develops complications from SCD, it also makes sense not to transfuse them with RBCs with additional Hgb S. Therefore, many laboratories will do a simple solubility test, as described earlier, and select units that lack Hgb S. Realize that individuals with SCD are anemic and cannot serve as blood donors, however, there are active donors with sickle cell trait.

Leukoreduction (LR) of blood products has been proven to reduce the risk of cytomegalovirus (CMV) transmission, reduce the risk of febrile non-hemolytic transfusion reactions, and reduce the risk of human leukocyte antigen (HLA) alloimmunization. There are also studies, though controversial, that show there are deleterious immunologic sequelae of transfusion that are prevented by reducing the load of WBCs in transfused blood products. Since patients with SCD are chronically transfused, many believe that these patients should receive LR blood products. Of note, there is also a study that shows reduced rates of RBC alloimmunization in patients who receive LR blood products. Transfusion recommendations for patients with SCD are:

- Blood products that are sickle hemoglobin negative
- Blood products that are leukoreduced
- Blood products that are negative for C, E, and K1 antigens if the patient lacks these antigens
- Blood products that are negative for any additional antigens against which the patient has antibody
- Blood products that are from African American donors, if a program exists

Summary

The substitution of one amino acid in the hemoglobin molecule results in sickle hemoglobin. As a result, RBCs sickle in low oxygen states causing occlusion of blood vessels, increased viscosity, and inflammation. These RBCs are prematurely removed from the circulation, resulting in a chronic hemolytic anemia. With newborn screening and early treatment, the death rate among children with SCD has declined. In addition, a variety of treatments are being introduced to help manage the various manifestations of disease. Transfusion, simple or exchange, is a mainstay of therapy, since it reduces the amount of Hgb S in circulation and suppresses erythropoiesis. Transfusion is indicated for symptomatic anemia and specifically to prevent stroke (first or recurrent), during acute stroke, and for acute chest syndrome. Unfortunately, transfusion carries risks for in-
fectious disease transmission, as well as immunologic and inflammatory sequelae. For patients with SCD who may be chronically transfused, iron overload occurs frequently. In addition, due to differences in RBC antigens between donors and recipients, these patients are at increased risk for development of RBC alloantibodies, which can complicate further transfusion. It is, therefore, important to prevent alloimmunization by transfusing leukoreduced RBCs that match the patient for the C, E, and K1 antigens. Human progenitor cell (from bone marrow, peripheral blood stem cells, or umbilical blood) transplant can cure the disease, and is used for patients with severe disease for whom conventional therapy may not be effective.

References
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46. Blumberg N, Heal JM, Gettings KF. Leukoreduction of red cell transfusion is associated with a decreased incidence of red cell alloimmunization. Transfusion 2003;43:945–52.

Additional Resources

Susan D. Roseff, MD, Medical Director, Transfusion Medicine, Professor, Virginia Commonwealth University, Department of Pathology, PO Box 980662, Richmond VA 23298-0662.

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