TRANSFUSION MEDICINE

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LEARNING OBJECTIVES

Upon completion of this exercise, the participant will be able to

- identify populations at risk for sickle cell disease (SCD).
- describe the pathophysiologic mechanisms of the SCD process.
- provide clinical management of the vasoocclusive complications of SCD.
- diagnose hyperhemolysis syndrome as a possible complication of SCD.
- discuss the clinically accepted indications for acute exchange transfusion therapy in patients with SCD.
A 20-year-old black woman was admitted to the hospital and treated for pain crises. She had sickle cell anemia with sickle cell disease (SCD), was enrolled in the hospital’s red blood cell (RBC) exchange transfusion program, and was followed up by both the hematology and transfusion medicine services. Her medical history was also significant for a stroke approximately 1 year previously, acute chest syndrome, hyperhemolytic syndrome, and depression. The patient had multiple admissions to the hospital, primarily for sickle cell pain crises.

The patient had a smoking history of one-third pack of cigarettes per year for 4 years. She denied alcohol consumption and illegal drug use. Her medications included defesasirox (an oral iron chelator), hydromorphone, aspirin, folic acid, hydroxyurea, sertraline for depression, and medroxyprogesterone for contraception. Her surgical history was unremarkable. She was allergic to sulfa-containing medications and strawberries. Her parents and siblings were all alive and relatively healthy. The patient’s current laboratory values are shown in Laboratory Data.

### Laboratory Data

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Patient Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, (\times 10^3/\mu L)</td>
<td>13.6 (13.6)</td>
<td>4.0-11.0 (4.0-11.0)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL (g/L)</td>
<td>7.8 (78)</td>
<td>12.0-15.0 (120-150)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>22.9</td>
<td>34-44</td>
</tr>
<tr>
<td>Platelet count, (\times 10^3/\mu L)</td>
<td>409 (409)</td>
<td>170-404 (170-404)</td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>136 (136)</td>
<td>135-145 (135-145)</td>
</tr>
<tr>
<td>Chloride, mEq/L (mmol/L)</td>
<td>107 (107)</td>
<td>98-109 (98-109)</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L (mmol/L)</td>
<td>24</td>
<td>22-31</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL (mmol/L)</td>
<td>5 (1.79)</td>
<td>7-21 (2.50-7.50)</td>
</tr>
<tr>
<td>Creatinine, mg/dL ((\mu mol/L))</td>
<td>0.6 (53)</td>
<td>0.6-1.2 (53-106)</td>
</tr>
<tr>
<td>Glucose, mg/dL (mmol/L)</td>
<td>98 (5.44)</td>
<td>65-110 (3.61-6.11)</td>
</tr>
<tr>
<td>Sickle cell hemoglobin (HbS), %</td>
<td>75.7</td>
<td>0</td>
</tr>
<tr>
<td>Ferritin, ng/mL (pmol/Lng/mL)</td>
<td>3490 (7842)</td>
<td>10-322 (22.5-723.5)</td>
</tr>
<tr>
<td>Bilirubin, total, mg/dL ((\mu mol/L))</td>
<td>3.2 (54.7)</td>
<td>0.2-1.3 (3.4-22.2)</td>
</tr>
</tbody>
</table>
MANAGEMENT OF SICKLE CELL DISEASE 
AND ITS COMPLICATIONS

Distribution and Epidemiology of SCD
SCD is the most common genetic disease affecting humans. The prevalence of 
the sickle cell gene is estimated to be 8% in blacks, with 1 in 500 homozygous 
for hemoglobin SS disease.1 Although SCD primarily involves persons of African 
descent, it is also seen in persons of Middle Eastern and Asian descent. The highest 
frequency of the sickle gene is in equatorial Africa, although it may be found virtually 
worldwide. Patients with the sickle cell trait (heterozygous hemoglobin S [HgS]) are 
found in Italy, Greece, the Middle East (particularly Saudi Arabia), India, northern 
Europe, Australia and New Zealand, Southeast Asia, North and South America, and 
the Caribbean islands. The spread of the sickle cell gene is partly due to migration 
and the slave trade that occurred between the 16th and 18th centuries. Because of 
its global distribution, management of SCD is an international effort.2 The financial 
costs of SCD are staggering. Total annual cost exceeds $US1.1 billion for the 70,000 
persons with SCD in the United States according to one estimate. This figure 
includes medications, transfusions, and hospitalizations.3

Pathophysiology
An abnormal hemoglobin (Hb) molecule, HbS, rather than the normal HbA, results 
from a single point mutation of valine for glutamine at the sixth amino acid position 
of the β globin gene. When HbS becomes deoxygenated, it becomes less soluble 
and subsequently forms polymers. Polymerization increases the rigidity of the RBC 
membrane and causes sickling of cells.4

The marked variability in the presentation of symptoms in patients with SCD 
indicates a more complex disease than explained by a single-point amino acid 
substitution.5 Current research reveals the involvement of endothelial dysfunction, 
inflammatory processes, and possibly coagulation abnormalities. The significance 
of decreased levels of nitric oxide has recently been demonstrated. Nitric oxide 
is an important mediator of vasodilation and platelet activation/aggregation. It is 
scavenged within the blood by the heme molecule, in addition to playing a role 
in enzymatic conversion of L-arginine to ornithine by erythrocyte arginase. Under 
normal physiologic conditions, only a small amount of free hemoglobin is present in 
the plasma. Consequently, only minimal scavenging of nitric oxide molecules occurs. 
When hemolysis increases, as in SCD, the increased plasma hemoglobin level results 
in increased binding and destruction of nitric oxide. This is becoming one of the 
central tenets in the understanding of how the disease manifests clinically. As a result 
of reduction in nitric oxide, patients with SCD become prone to vasoconstriction and 
vascular thrombosis. In addition, both the heme molecule and free hemoglobin have 
been postulated to have proinflammatory effects.5

Clinical Complications of SCD and Current Management
The 2 main pathologic consequences of sickled RBCs are vasoocclusion and 
hemolysis. Obstruction of the microcirculation results in tissue ischemia, while
anemia results when the rate of hemolysis is not balanced by RBC production within the bone marrow. The main clinical complications of SCD are summarized in the Table.

**Pain Crises**
Acute pain crises are the most frequent cause of emergency department visits and hospitalizations among patients with SCD. Precipitants of pain crises include fever, acidosis, and infection.

The onset of pain is initiated by muscular and soft tissue ischemia as a result of vasoocclusion by sickled cells. It commonly affects the extremities, back, and ribs. Interestingly, the pattern of pain is relatively consistent. One of the main goals of treatment is adequate hydration using at least 3 to 4 L of either oral or intravenous fluids per day, along with supplemental oxygen to correct the existing hypoxia.

Analgesics are used for pain relief. Moderate-to-severe painful episodes require narcotic medications such as morphine, which can be given 0.3 to 0.6 mg/kg orally every 4 hours or 0.1 to 0.15 mg/kg intravenously every 4 hours.

Patients who have recurrent and uncontrolled pain crises may benefit from RBC exchange transfusions or hydroxyurea. Routine RBC transfusion is generally not indicated in the acute setting because the increased hematocrit levels may exacerbate the condition. Although patients who are chronically transfused may report fewer pain crises, no prospective data have proven the benefits of transfusion for prevention of crises. Therefore, transfusion therapy is not considered the standard of care in patients with SCD.

The effectiveness of hydroxyurea in increasing HbF levels, as well as decreasing pain crises, acute chest syndromes, hospitalizations, transfusions, and even mortality has been borne by several studies, most notably the Multicenter Study of Hydroxyurea randomized clinical trial. Indications for the use of hydroxyurea are moderate to severe disease, especially for those patients with recurrent vasoocclusive events. The initial dose of hydroxyurea is usually 15 mg/kg/day up to a maximum of 35 mg/kg/day. It is available in both capsule and tablet forms, with amounts ranging from 100 mg to 1000 mg. Potential side effects include neutropenia, anemia, and thrombocytopenia. However, these hematologic changes tend to be reversible following discontinuation of the drug. Frequent laboratory monitoring with a complete blood cell count is recommended. Hyperpigmentation of the skin and changes in nails may occur. Concern about the development of malignancy, particularly leukemia, has been raised, but a recent Agency for Healthcare Research

<table>
<thead>
<tr>
<th>Vasoocclusive Complications</th>
<th>Other Complications</th>
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<tbody>
<tr>
<td>Stroke</td>
<td>Hyperhemolytic syndrome</td>
</tr>
<tr>
<td>Pain crises</td>
<td>Iron overload</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td></td>
</tr>
<tr>
<td>Priapism</td>
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and Quality review suggested that this may not be the case. Despite the efficacy of hydroxyurea, multiple obstacles to its use remain, including both a general lack of knowledge of it as a treatment option, as well as concerns about its side effects.

**Stroke**
Red blood cell exchange transfusion therapy can be used both as an acute and as a prophylactic treatment for stroke. Chronic transfusion therapy has been proven to be efficacious in preventing and lowering the incidence of stroke in patients with SCD. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) demonstrated that maintaining an HbS level of less than 30% lowered the initial stroke rate by 92%. The follow-up study, STOP-2, showed that discontinuation of the prophylactic transfusion regimen led to reversion to abnormal transcranial Doppler velocities and stroke.

**Acute Chest Syndrome**
Dyspnea, fever, chest pain, hypoxemia, and an abnormal chest radiograph characterize acute chest syndrome (ACS), one of the complications of SCD that typically requires emergent exchange transfusion, although simple transfusion has been used as well. Radiographic findings reveal a new infiltrate, a segmental increase in infiltrate size, or both. It may be secondary to infection, infarction, or fat embolism. Exchange transfusion optimizes the oxygen transport while avoiding increased blood viscosity. It is appropriate in cases of acute chest syndrome that do not respond to simple transfusion, have extensive lung involvement, or present with hypoxemia that does not respond to simple oxygen therapy or requires ventilatory support. The goal of the procedure is to reduce the postexchange HbS value to 30% or less.

**Stem Cell Transplantation**
The only treatment option that may offer a cure for SCD is a stem cell transplant. Successful use of nonmyeloablative stem cell transplant has been performed. In a study of adult patients who underwent allogeneic stem cell transplant using a nonmyeloablative conditioning regimen that included alemtuzumab, sirolimus, and total body irradiation (300 cGy), the cohort showed significant improvement in hematologic parameters. In addition, no evidence of mortality was noted at the median follow-up of 30 months. Graft-vs-host disease was not observed in any of the treated patients, and side effects were seen as manageable and of low toxicity.

**Hyperhemolysis**
Pain, fever, and laboratory features such as hemoglobinemia, hemoglobinuria, increased lactate dehydrogenase level, and reticulocytopenia are the common accompanying signs/symptoms of hyperhemolysis. Hyperhemolysis is a known complication of transfusion in patients with SCD. Clinically, it is characterized by a sudden and severe drop in hemoglobin level, usually following transfusion, and hemoglobin levels decrease to pretransfusion levels. Hyperhemolysis can also occur in the absence of transfusion, usually in the setting of acute pain crises as well as in non-SCD cases, including thalassemia, anemia of chronic disease, and myelofibrosis.

In the process of hyperhemolysis both donor (transfused) and recipient RBCs are hemolyzed. The exact pathophysiology of this process is unknown. Among the proposed theories, Petz and Garatty described a “bystander phenomenon” in which
antibodies to human leukocyte antigens and plasma proteins lead to macrophage activation and subsequent hemolysis. Treatment strategies for hyperhemolysis include steroids, intravenous γ-globulin, rituximab, erythropoietin, and avoidance of RBC transfusion with the exception of clinically significant anemia or life-threatening hemorrhage.

**Priapism**
Up to 89% of men with SCD experience priapism, an unwanted and prolonged erection lasting longer than 2 to 4 hours. The first episode likely occurs by age 20. The mechanism is venous outflow obstruction of the corpora cavernosa, with sickled RBCs. Repeated episodes can have deleterious sequelae; the most common are impotence and corporeal fibrosis. Initial management includes intravenous hydration, analgesics, and urinary alkalinization. However, urologic/surgical intervention, including aspiration and irrigation of the corpora cavernosa, is warranted if conservative measures fail or the erection persists longer than 4 hours. Emergent RBC exchange transfusion has been used to treat priapism when urologic measures fail. This approach should be taken with caution due to the Association of Sickle Cell Disease, Priapism and Exchange Transfusion and Neurologic Events (ASPEN). ASPEN syndrome refers to the acute onset of neurologic complaints including hemiparesis, coma, seizures, and headache, from 1 to 11 days postexchange. ASPEN syndrome is treated with simple transfusion.

**Iron Overload**
In patients with SCD who receive transfusions for the long term, iron overload may occur. It usually begins after at least 100 mL/kg of RBCs have been transfused; this corresponds to approximately 20 units of packed RBCs. Transfusion-related iron overload, like other hemosideroses, can lead to multiorgan failure, involving the liver, heart, and/or pancreas. Iron chelation therapy is the standard of treatment. Intravenous deferoxamine has been the gold standard of chelation. The recent development of oral iron chelators, such as deferasirox, offer hope of improved patient compliance. The usual starting dose is starting 20 to 30 mg/day, which is gradually increased to 40 mg/kg/day. Common adverse effects include skin rash, gastrointestinal upset, including nausea and vomiting, and increased serum creatinine level.

Decreased iron overload has been advocated as an advantage of chronic RBC exchange transfusion therapy in patients with SCD. It is classified as a Category II indication for treatment of iron overload in the current apheresis guidelines established by the American Society for Apheresis, although recommendations have been made to reclassify it as Grade IC.

**Future Therapies**
With increased understanding of the pathophysiology of SCD, new drugs have been developed. These medications act on several of the purported mechanisms of SCD, namely HbF induction, RBC hydration, nitric oxide bioavailability, and antiinflammatory effects. Examples of these newer drugs include butyrate, decitabine, nitric oxide, tinzaparin, and eptifibatide.
REFERENCES