SICKLE CELL DISEASE: Current State, Upcoming Advances, and How to Manage Patients with This Disease Effectively

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BACKGROUND
Sickle cell disease (SCD) is a chronic genetic disorder caused by a mutation that results in the production of abnormal hemoglobin (Hb), referred to as sickle hemoglobin (HbS), in red blood cells (RBCs). Deoxygenated HbS polymerizes into rigid fibers resulting in a physically deformed sickled RBC with structural and functional deficits. The disease affects 100,000 individuals in the United States, including 1 of every 365 African-Americans.

Sickle cell disease is characterized by chronic hemolytic anemia, painful episodes of vascular occlusion, and multi-organ damage. Clinical severity is variable; however, many patients require frequent emergency department (ED) visits and hospitalizations, most of which are the result of vaso-occlusive episodes (VOEs)—unpredictable, painful episodes caused by transient vascular occlusion by sickled RBCs and impaired blood flow resulting in localized ischemia-reperfusion injury. Vascular complications, most prominently stroke, but also including a broad range of macrovascular and microvascular complications affecting not only the brain, but also the heart, lungs, kidneys, and other organs, are common in these patients. The clinical manifestations of SCD result in a quality of life that is worse than that of patients with cystic fibrosis and comparable to hemodialysis patients.

Measures such as newborn screening, immunizations, and prophylactic penicillin have resulted in improved outcomes. However, the average life expectancy of the patient with SCD remains only 40 to 50 years. Few options are available for the management of SCD; primary treatments include hydroxyurea and transfusions. A small percentage of patients qualify for potentially curative allogeneic stem cell transplant.

The chronic pain of SCD is complex and multifactorial. This leads to reduced understanding of the pain experience by health care providers and discord in the patient-provider relationship, which can ultimately impact the provision of adequate care. Case managers can provide high value in this setting by coordinating care and acting as advocates for these patients.

This review examines the clinical impact of SCD and discusses current and upcoming therapeutic interventions to assist case managers in coordinating effective management for these patients.

THE PATHOPHYSIOLOGY OF SICKLE CELL DISEASE
Sickle cell disease is caused by a mutation in the β-globin gene. There are several different genotypes of SCD, the most severe of which is sickle cell anemia (HbSS), in which individuals inherit 1 sickle gene from each parent. This mutation creates a hydrophobic region in deoxygenated HbS that promotes polymerization, resulting in an abnormally shaped RBC that is adherent and no longer deformable, resulting in a propensity to physically block the microvasculature.

Repeated cycles of vaso-occlusion, impaired tissue oxygenation, and subsequent reperfusion damage affected tissues and promote ongoing injury to the inner lining of the blood vessels, including an increased propensity for RBCs and white blood cells (WBCs) to adhere to the lining and activate each other, further exacerbating vaso-occlusion.

Sickle hemoglobin polymers are toxic to RBCs and cause hemolysis; the average sickle RBC survives only 10 to 20 days vs about 120 days for normal RBCs. Along with causing anemia, hemolysis results in the release of the intracellular contents of RBCs. Free Hb scavenges nitric oxide (a critical regulatory gas that modulates vascular tone), promoting vascular dysfunction. These, and other pathways, contribute to an ongoing inflammatory state and a high level of oxidative stress in patients with SCD.
CLINICAL MANIFESTATIONS OF SICKLE CELL DISEASE

While a complete review of the many clinical manifestations of SCD is beyond the scope of this manuscript, Table 1 provides an overview of the most common complications of SCD.

Infants can manifest symptoms of SCD as early as 6 months, presenting with painful swelling of the hands and feet, infection, anemia, jaundice, or an enlarged spleen. Because children are at higher risk for infections, immunizations and prophylactic penicillin are life-saving interventions initiated in early life.

Although most acute pain episodes are managed at home, acute VOEs are the most common reason for hospitalization in SCD. Episodes may be managed with opioids or nonsteroidal anti-inflammatory drugs (NSAIDs). Acute pain episodes peak between the ages of 20 and 29. Patients seek care for only the most severe episodes, and thus their frequency may be underestimated.

Acute chest syndrome, which often follows a VOE, is the second most common reason for hospital admission. Its severity increases with age, with >10% of adult cases resulting in fatalities or severe complications as a result of associated multiorgan failure or a neurologic event. Hospitalized patients with acute chest syndrome are managed with a combination of antibiotics, bronchodilators, incentive spirometry, oxygen supplementation, and transfusions.

Stroke is common in patients with SCD and is a major cause of mortality. Children with specific SCD genotypes (HbSS, HbS-beta-thalassemia-0) have a 300-fold higher risk of stroke compared with unaffected children, and 1 in 4 adults with SCD will suffer a stroke by the age of 45. Silent cerebral infarcts, defined as abnormal magnetic resonance imaging of the brain in the setting of a normal neurologic examination and without a history or physical findings associated with an overt stroke, occurs in 27% of patients by age 6 and 37% by age 14. Transcranial Doppler (TCD) measurement of blood flow velocity in the blood vessels supplying the brain is used to screen for stroke risk in children and to identify patients in whom prophylactic long-term transfusion is appropriate to reduce risk. Patients with SCD who have an overt stroke are treated emergently with exchange transfusion, followed by chronic transfusion to prevent recurrence.

Sickle cell disease promotes a thrombotic phenotype that predisposes patients to venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism. As a result, up to 12% of SCD patients may experience VTE by the age of 40. Episodes of VTE are often recurrent and associated with increased mortality.

Other clinical complications in patients with SCD include, but are not limited to, priapism, gallstones, leg ulcers, and osteomyelitis. Acute anemic events may occur, most commonly aplastic crises, hyperhemolytic crises, and acute splenic sequestration crises; acute splenic sequestration crisis is a potentially fatal complication that occurs in up to 30% of young children.

Survival has improved for SCD patients in the United States in recent decades, largely because of preventative measures for children and other advances in care; however, patients with SCD still have a reduced life span. Bacterial infections are a major cause of mortality in children with SCD, although rates have declined considerably over time because of a combination of antibiotic prophylaxis and optimization of immunizations. Early mortality can be the direct or indirect result of acute and chronic complications such as organ failure, acute chest syndrome, infection, stroke, or acute right heart failure.

Sickle cell disease is a biopsychosocial disease and is a profoundly clinically consequential and complex disease state. Management should be intensive and address the entire spectrum of risks faced by these patients. Given the fragmentation of health care and the unmet need for multispecialty management for these patients, case managers can...
DISEASE MANAGEMENT FOR SICKLE CELL DISEASE

Clinical management involves routine prophylactic treatment and emergency care and is highly resource- and time-intensive. As more patients survive into adulthood, the difficulties of managing SCD are compounded by accumulating disease complications and comorbidities.

Hydroxyurea was, for over 2 decades, the only U.S. Food and Drug Administration (FDA)-approved pharmacologic treatment for SCD. Current guidelines suggest that hydroxyurea should be offered to all children with HbSS or HbS/β-thalassemia aged >9 months, regardless of clinical severity. Hydroxyurea reduces mortality and decreases the frequency of VOEs and acute chest syndrome by increasing production of fetal hemoglobin (HbF), which is protective against sickling. Hydroxyurea also decreases leukocyte count and has antiadhesive properties that may contribute to its clinical benefit. While currently the most effective drug available, hydroxyurea has a number of potential side effects, including rash, alopecia, nail discoloration, headache, nausea, and weight gain, as well as concerns about oncogenicity, all of which may influence adherence to therapy. L-glutamine was the second pharmacologic agent approved for use in SCD. It was approved in 2017 to reduce the acute complications of SCD in adults and children aged ≥5 years. It may act by reducing oxidant burden in SCD erythrocytes. In clinical trials, patients taking L-glutamine reported fewer VOEs compared with patients taking placebo, and the effects of L-glutamine were consistent regardless of whether the patients received concomitant hydroxyurea. Red blood cell transfusions can be both prophylactic and therapeutic depending on the setting in which they are used. They are indicated for treatment of acute stroke or acute chest syndrome and in the preoperative setting to reduce the risk of postoperative complications. Chronic transfusion therapy is indicated for prevention of primary or recurrent stroke. Iron overload, potentially leading to organ damage and often requiring iron chelation therapy, is a major issue for patients who receive frequent transfusions. Alloimmunization, in which the patient develops an immune response to donor antigens, results in reactions that complicate between 4% and 11% of transfusions for SCD. The only accessible curative therapy is hematopoietic stem cell transplantation, which replaces the patient’s hematopoietic stem cells with cells from a donor. This treatment is dependent on the availability of a suitable donor, generally a matched sibling (although the use of matched unrelated donors and haploidentical donors is being explored), and is a time-intensive, rigorous, and potentially high-risk procedure. There are a number of novel therapies for SCD currently in late-stage development that may be integrated into the treatment paradigm for SCD patients in the near future. These agents act on the proximal polymerization event or the more distal event of RBC adhesion to vasculature lining.

Voxelotor directly targets HbS polymerization by binding to Hb, changing its affinity for oxygen and reducing the amount of deoxygenated HbS available for polymerization. Voxelotor is a once-daily oral agent that was evaluated in a phase 3 trial conducted in 274 patients aged ≥12 years with Hb levels from ≥5.5 to ≤10.5 g/dL and 1 to 10 vaso-occlusive crises in the previous year; approximately two-thirds of patients were taking concomitant hydroxyurea. Increases in Hb of ≥1 g/dL were observed in 51% of patients in the voxelotor 1500-mg group (95% CI, 41-61), 33% of the voxelotor 900-mg group (95% CI, 23-42), and 7% of the placebo group at week 24 (95% CI, 1-12) (P<0.001 for voxelotor 1500 mg vs placebo). The incidence of vaso-occlusive crises was numerically reduced in both voxelotor groups, from 3.19 per person-year in the placebo group to 2.77 and 2.76 in the 1500-mg and 900-mg groups, respectively. The percentage of patients with an adverse event that occurred or worsened during the treatment period was similar across treatments; adverse events of grade 3 or greater were observed in 26%, 23%, and 26% of the voxelotor 1500 mg, voxelotor 900 mg, and placebo groups, respectively. Most adverse events were unrelated to the trial drug or placebo. An open-label extension study of this trial is ongoing.

Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin, blocking its interaction with P-selectin glycoprotein ligand-1 (PSGL-1) and inhibiting WBC and RBC adhesion to the vascular endothelium. It is a once-monthly intravenously infused drug that was evaluated in a double-blind, randomized, placebo-controlled, phase 2 trial in 198 patients; the primary endpoint was the annual rate of sickle cell-related pain crises among participants receiving high-dose therapy vs placebo. Among patients who received high-dose crizanlizumab, the median rate of crises per year was 45.3% lower, falling from 2.98/year with placebo to 1.63/year with crizanlizumab. Serious adverse events were reported at the same rate in the high-dose crizanlizumab and placebo groups. Adverse events that occurred in ≥10% of participants in either active treatment group and at a 2-fold or greater frequency than placebo included arthralgia, diarrhea, pruritus, vomiting, and chest pain.
Potentially curative emerging gene therapies are currently under investigation for use with patients with SCD. The advantage of these therapies is that the stem cells of the affected individual are used, removing the need for a suitable donor and the risk of complications from a bone marrow transplant. Recent advances in gene editing technologies have allowed for genetic manipulation studies, with multiple reports of successful outcomes. This potential treatment is still in early stages of development and requires further investigation to assess its long-term effects.28

**BARRIERS TO DISEASE MANAGEMENT IN SICKLE CELL DISEASE**

Primary care physicians are often the only resource for patients with SCD.9 However, many primary care physicians have only limited experience with SCD.10 Patients with SCD encounter barriers to care in the ED. One survey conducted by the National Heart, Lung, and Blood Institute (NHLBI) assessed barriers to care among ED providers in North Carolina. The study interviewed participants about their knowledge of the NHLBI guidelines for the management of VOEs. Although most providers reported being aware of the guidelines, >70% were unfamiliar with the NHLBI recommendations for management of VOEs. This lack of knowledge strongly suggests that guidelines are underutilized. Providers in the same study advocated for use of individualized protocols prepared by the patients’ hematologists or primary care providers; however, they indicated that these records are difficult to access for patients whose doctors are not affiliated with the hospital at which the patient presents.36

Patients with SCD may suffer the consequences of explicit and implicit racial bias and disease stigma related to frequent hospital visits. Patients living in chronic pain are more likely to be labeled “drug seekers” by distrustful health care providers and may not receive appropriate pain management.10,36 The NHLBI study found that providers were more willing to prescribe opioids to cancer patients and those with other comorbidities than to SCD patients with pain.36 All of these factors may discourage SCD patients from pursuing appropriate care.

Physicians may have difficulty managing the follow-up appointments and complex advanced therapies that are needed to improve patient outcomes in SCD.10 The NHLBI study found that ED physicians were unable to schedule follow-up appointments with primary care providers or hematologists for their SCD patients because of high patient volumes and time limitations. Electronic referral systems may provide additional support; however, these systems do little to manage patient adherence.36 In addition to the issues outlined above, as therapy improves for SCD, more patients than ever are living to adulthood; thus, transitioning from pediatric to adult care is an increasingly common challenge.12

**THE ROLE OF THE CASE MANAGER IN SICKLE CELL DISEASE**

Optimizing the care of patients with SCD has the potential to reduce the incidence of VOEs (which are ranked by most patients with SCD as the most significant symptom of the disease) and improve long-term outcomes. Given the complexity of SCD, case managers have the potential to dramatically improve outcomes by coordinating care and advocating for patients.10,37 Management of SCD demands a complex schedule of physician appointments, medication adherence, vaccinations, and repeat medical treatments, and the case manager is often the only consistent member of the health care team available to the patient. Case managers can help educate patients on how to use self-care strategies and encourage them to communicate effectively with health care providers. This knowledge can help empower SCD patients as they navigate through the health care system and can allow for more positive experiences with providers who are in the position to help them address the multiple clinical issues associated with SCD.10

**CONCLUSIONS**

Sickle cell disease is a chronic genetic illness requiring lifelong management. Although the life span for patients with SCD has increased in recent decades, there are significant barriers to appropriate care that not only reduce the quality of care for these patients but may also actively discourage patients from pursuing adequate care and appropriate pain management. Case managers can play an important role in improving disease outcomes by advocating for SCD patients, coordinating care, and bridging patient and provider deficits in knowledge.

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References available online.
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Questions

1. Sickle cell disease is a chronic genetic disorder caused by a mutation that results in the production of abnormal hemoglobin.
   a. True
   b. False

2. How many African Americans in the United States are affected by sickle cell disease?
   a. 1 of every 325
   b. 1 of every 345
   c. 1 of every 365
   d. 1 in every 486

3. Sickle cell disease is characterized by:
   a. Chronic hemolytic anemia
   b. Painful episodes of vascular occlusion
   c. Multiorgan damage
   d. All of the above

4. Vascular complications include a broad range of macrovascular and microvascular complications affecting the:
   a. Brain
   b. Heart
   c. Kidney
   d. All of the above

5. The average life expectancy of patients with sickle cell disease is:
   a. 20 to 25 years
   b. 25 to 30 years
   c. 30 to 40 years
   d. 40 to 50 years

6. Infants with sickle cell disease can manifest which of the following symptoms as early as 6 months?
   a. Painful swelling of hands and feet
   b. Infection
   c. Anemia
   d. All of the above

7. Sickle cell disease is a biopsychosocial disease and is a profoundly clinically consequential and complex disease state.
   a. True
   b. False

8. Treatment for sickle cell disease may include:
   a. Hydroxyurea
   b. L-glutamine
   c. Red blood cell transfusions
   d. All of the above

9. The only accessible curative therapy for sickle cell disease is hematopoietic stem cell transplantation.
   a. True
   b. False

10. Barriers to disease management in sickle cell disease include:
    a. Physicians with limited knowledge of sickle cell disease
    b. Explicit and implicit racial bias
    c. Physicians having difficulty managing follow-up appointments
    d. All of the above
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Objectives: November 2019

1. State the pathophysiology of sickle cell disease. ____________________________
2. State three treatments for sickle cell disease. ____________________________
3. State three barriers to disease management in sickle cell disease. ____________________________
4. Define the role of the case manager in sickle cell disease. ____________________________

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