Statement on Sickle Cell Disease

Student National Medical Association
Health Policy and Legislative Affairs Committee
Statement on Sickle Cell Disease

First Edition

Originally authored and prepared for the 2019 AMEC BOD Session
April 18-21, 2019
Philadelphia, PA

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INTRODUCTION

The Student National Medical Association (SNMA) represents thousands of underrepresented minority medical students committed to addressing the needs of underserved communities and increasing the number of clinically excellent, culturally competent, and socially conscious physicians. With that mission in mind, the SNMA has long recognized those with Sickle Cell Disease (SCD) as a group that has historically been underserved both in terms of availability and quality of medical treatment and funding for research to investigate the causes and potential treatments for SCD.

SCD is a term used to describe a group of disorders characterized by a genetic mutation leading to Hemoglobin S (HbS) that includes Sickle Cell Anemia and other hemoglobinopathies with a combination of other gene mutations in addition to HbS including Hemoglobin SC Disease and Hemoglobin SB Thalassemia. Sickle Cell Anemia is an inherited red blood cell disorder that affects approximately 100,000 Americans, most commonly people with ancestors from sub-Saharan Africa. The mutation causes characteristic red blood cell sickling due to production of HbS resulting in severe complications if an individual is homozygous for the mutation. Individuals who are heterozygous with one sickle cell gene and one normal gene are known as carriers and usually experience no symptoms unless they face extreme conditions compromising their oxygen state such as severe dehydration or high-intensity physical activity.^{1}

Complications of the disease stem from both the oxygen carrying capacity of mutated hemoglobin as well as changes to red blood cells in low oxygen conditions. Primarily, the major complications that are seen in individuals with SCD include pain crises, anemia, and infection.^{2}

Treatment options typically used to manage SCD are very few in number and include pain medications to relieve pain during vaso-occlusive episodes, blood transfusions in the case of severe anemia or sudden severe illness, the FDA-approved medication Hydroxyurea, and bone marrow transplant which is currently the only curative therapy.^{2}

According to the 2016 Report of the State of Sickle Cell Disease and the following 2018 Report Card for the State of Sickle Cell Disease created by the American Society of Hematology (ASH), some of the major issues today in medical care for individuals living with SCD in the United States are limited access to medical care, lack of health care providers with comprehensive knowledge and expertise to care for individuals with SCD, and barriers to patient
participation in research and clinical trials.\textsuperscript{3} The SNMA recognizes that much work still needs to be done in these priority areas and continues to advocate for improving access to care and quality of care while encouraging the development and continuation of initiatives and legislation to improve health disparities for those living with SCD. The purpose of this policy statement is to provide an assessment of the contributing factors to disparities in care for those living with SCD and discuss the SNMA’s position and recommendations for strategies to improve those disparities.

**BACKGROUND**

SCD affects millions of people throughout the world. In the United States, most people living with SCD are of sub-Saharan African descent with a rate of SCD occurring in 1 out of every 365 Black or African-American births. Other groups of people living in the US suffering from SCD include those with ancestors from Spanish-speaking regions in the Western Hemisphere, Saudi Arabia, India, and some Mediterranean countries including Turkey, Greece, and Italy.\textsuperscript{4}

Historically, the disease has been incorrectly labeled as a “Black Disease” because of the disproportionate number of people of African descent affected by it. However, research has shown that distribution of the mutation causing the disease shows predominance in equatorial Africa and shows high frequency in other malaria-prone areas as well including the tropical countries mentioned above. To date, there are three major hypotheses regarding the advantage of the HbS mutation in the setting of malaria infection: (1) red blood cells containing HbS are less supportive of malaria infection than normal red blood cells under low oxygen conditions, (2) infected red blood cells containing HbS have difficulty adhering to vessel walls which has been implicated in the process of evasion from the immune system, and (3) infected HbS containing red blood cells are more easily removed from circulation because of inherent structural deficiencies.\textsuperscript{5}

The mutation that leads to HbS is a classically studied genetic mutation of hemoglobin – the protein that carries oxygen in red blood cells. This mutation is a single nucleotide substitution in the B-globin gene that encodes a change in amino acids from Glutamate to Valine. However, complications from this mutation only arise when an individual inherits both recessive HbS genes from his/her parents.\textsuperscript{6}
The complications of the disease primarily stem from the physiologic changes to affected red blood cells in low oxygen conditions. Under these conditions, red blood cells homozygous for the HbS mutation form hemoglobin polymers that change the physical architecture of red blood cells into a sickle shape from which the disease gets its name. These cells are rigid and can stick to vessel walls causing clustering that may result in a blockage that slows or stops blood flow anywhere in the body. When this occurs, oxygen delivery to nearby tissues decreases significantly and can cause attacks of acute and severe pain called vaso-occlusive episodes (aka pain crises) that often require individuals to go to the hospital for adequate pain management. Likewise, because of the architectural changes to red blood cells in low oxygen conditions, they tend to have shorter life spans than the average red blood cell in an individual without SCD causing the body can have difficulty keeping up with the pace of destruction of these cells – a process called hemolysis. As a result, the number of red blood cells in a person living with SCD is lower than average and anemia is a commonly seen.\textsuperscript{6}

Other major concerns for complications secondary to SCD include those linked to damage of the spleen – an organ tasked with immune defense and quality control of red blood cells. Repeated vaso-occlusive episodes targeting the spleen can cause fibrosis and eventual atrophy of the organ, a term called auto-splenectomy. Likewise, vaso-occlusive episodes targeting the spleen can also cause a severe acute condition called splenic sequestration due to the trapping of blood in the spleen leading to congestion and enlargement of the spleen which may cause hypovolemic shock due to lack of blood flow in the circulation and decreased oxygen delivery to the body. Individuals with impaired splenic function are at risk for severe and invasive infections with encapsulated bacteria including \textit{Streptococcus pneumoniae} and \textit{Hemophilus influenzae type B} (known causes of meningitis) as well as \textit{Salmonella} species which are a major cause of bone infections for patients living with SCD.\textsuperscript{6}

Of note, the most recent data regarding mortality rates in sickle cell anemia in the United States lists the median age of death as 42 years for males and 48 years for females. Bacterial infections are one of the leading causes of death for people living with sickle cell anemia at any age.\textsuperscript{7}

More recent studies looking at demographics (primarily prevalence and distribution of the disease), complications, and potential treatments have made SCD an improving field of research. To date, gene therapy is currently undergoing active clinical trials as a potentially
curative therapy with multiple other therapies in the research and development pipeline following behind. While historically funding for SCD has been provided by the National Heart, Lung, and Blood Institute (NHLBI) through the Comprehensive Sickle Cell Centers), the “Sickle Cell Disease Surveillance, Prevention, and Treatment Act of 2018” intended to create a national program for data collection, public health initiatives, and the identification and development of strategies for SCD prevention and treatment suggests that better funding and initiatives are on the horizon. However, continued advocacy is desperately needed to ensure funding becomes optimal in the future.

**SCOPE OF THE PROBLEM**

Awareness for SCD has improved dramatically with increased resources over the past forty years leading to advances in treatment methods for people living with the disease. These collective efforts have allowed the life expectancy for those living with SCD to rise from the mid-teens to the mid-forties. However, the average lifespan is still almost half of the average lifespan of an individual from the same racial background living without SCD. 8

Paralleling the high rates of early mortality for people living with SCD, morbidity is also staggeringly extensive and suggests underlying social determinants of health inequity. SCD is well known in the medical community for its relationship with high healthcare utilization measured by emergency department visits, hospitalizations, and hospital stay length. Adults living with the disease experience an average of almost three hospital encounters a year 9 and 29-40% of SCD-related ED visits result in hospitalization. 10 A closer evaluation of the factors leading to this high utilization of the healthcare system is warranted.

**Sociodemographic Factors**

Current research suggests that only a very small minority of people living with SCD account for most of the healthcare resource use. 9 Most patients self-manage the disease while a minority frequently require emergency care. Of the studies that have examined the backgrounds of patients linked to frequent use of the healthcare system, those that have addressed sociodemographic factors have been the most revealing.

Insurance type has been significantly associated with health care utilization and poor quality of life for both pediatric and adult patients. In the adult population, acute care encounters
and rehospitalizations are highest among the 18-30 year old age group and publicly insured patients.\textsuperscript{9} Medicaid and Medicare are known to be the major sources of funding for majority of hospital costs related to SCD so the implication that there is a difference between utilization of services when an individual has private vs. public insurance coverage is concerning. Research into the pediatric population has further delved into this matter by demonstrating no significant relationship between utilization and neighborhood distress which includes poverty rates for neighborhoods defined by zip code. However, in the same study, having public insurance was strongly related to disease outcomes.\textsuperscript{11}

Interestingly, for many studies looking at hospital utilization patterns for both pediatric and adult patients, the use of multiple sites of care for acute care treatment has also been a variable linked to rates of acute care encounters and hospitalizations. The use of multiple sites of care has been shown to have a relationship with increased rates of hospitalizations and SCD-related hospital encounters.\textsuperscript{12} While there hasn’t been much research into the reasons why patients might frequent multiple sites of care, it may be an indication of a lack of a centralized medical home for these patients which may be a contributor to increased medical costs due to dispersed and fragmented care. Notably, uninsured patients and patients with public insurance are more likely compared to their counterparts with private insurance to use multiple hospitals for acute care.\textsuperscript{13}

\textit{Treatment Options}

The options for the treatment for patients living with SCD are few in number and include pain management, transfusion services, the use of Hydroxyurea (HU), and bone marrow transplant. For those who are symptomatic or currently undergoing vaso-occlusive episodes, the mainstays are pain management and transfusion. HU, on the other hand, takes weeks to months to become effective so it is not used in acute settings and is instead used to prevent complications. Currently, hematopoietic stem cell transplant is the only curative therapy for this disease. With most of the available treatments currently being utilized being more reactive to complications as opposed to prevention, it is no surprise that the healthcare system is used more frequently to manage complications in acute settings.

The indications for red cell transfusion are clinical scenarios in the acute setting where there is a strong benefit of reduced morbidity when used. This includes severe anemia, stroke
prevention, and reduction of pain crises in the setting of severe or symptomatic anemia among other severe complications.\textsuperscript{14,15} However, the use of blood transfusion for these patients is not without risks. When receiving these treatments, patients are also at risk for complications of RBC transfusion such as transfusion reactions, alloimmunization, transfusion-related infection, and retention of excess iron.\textsuperscript{16}

Over 30 years ago, HU was introduced as a preventative measure against SCD. The medication works by increasing fetal hemoglobin (HbF) levels in the blood which contributes towards a reduction in vaso-occlusive episodes. Since emerging as the most affordable preventive effort against SCD, studies have shown that the use of HU has been linked with reductions in SCD mortality and improved patient outcomes if SCD is detected and treatment is started at an early age.\textsuperscript{17} To that point, the National Heart, Lung, and Blood Institute expanded their guidelines for pediatric indication for HU in 2014 to state that treatment should be offered to all children with SCD with treatment beginning at 9 months of age.\textsuperscript{18}

Despite the relative inexpensiveness and availability of HU, utilization is very low. Barriers to use of HU were addressed in a 2018 NIH Consensus Statement that discussed social barriers like poverty and insurance status as well as system-level barriers like financing, geographic isolation, lack of coordination between academic centers and community-based clinicians, transition from pediatric to adult care, and limited access to care among many other concerns.\textsuperscript{19}

The most promising research for a curative therapy for SCD originated from work surrounding bone marrow transplant from sibling matches to recipients, a process called allogeneic hematopoietic stem cell transplantation. This method, largely used in treatment in children, involves high doses of chemotherapy to suppress the recipient’s immune system before transferring donor stem cells. Patients are started on immunosuppressants after the procedure to prevent transplant rejection which comes with the risk of potentially harmful side effects including higher susceptibility to infection.\textsuperscript{20}

However, while allogeneic stem cell transplant is the only current curative therapy for SCD today, very few patients with SCD receive this treatment. When examining barriers to transplantation, the major issues of lack of financial or psychosocial support and lack of a candidate sibling donor often stop the process before HLA typing - the process used to match donors and recipients for bone marrow or cord blood transplants.\textsuperscript{20}
Pain Management and Stigma

Perhaps one of the most studied barriers to care in patients with SCD within the last decade, stigma in the setting of treating vaso-occlusive crises remains a major preventable contributor to poor quality of care in this patient population. In this acute setting, a significant factor contributing to health care disparities is the poor relationship between providers and patients in the healthcare system.

Research from the IOM in ethnic disparities in healthcare has further assessed the details from typical clinical encounters and point out bias/prejudice against minorities, clinical uncertainty when interacting with minority patients, and beliefs or stereotypes held by the provider about the behavior or health of minority patients as factors from the provider’s side leading to poor treatment outcomes. Patients, in response to provider biases, may react with mistrust in the healthcare system or by refusing treatment. However, with a disease like SCD where acute pain crises is part of the pathology, there is an inherent need for the healthcare system to address morbidity and reduce mortality rates. To be frank, when undergoing pain crises, not going to the hospital for pain management is simply not an option.

These same issues are thought to play a role in the quality of care for SCD patients provided in the emergency department (ED) setting. Research has shown that patients with SCD undergoing vaso-occlusive episodes that go to the ED for treatment are more likely to experience significant delays in time to be evaluated by a provider and to be administered pain medication despite being triaged higher due to presenting with severe pain. A direct link between provider attitudes and provider practices in treating SCD patients has been suggested and further studies have affirmed that theory by linking negative provider attitudes towards SCD patients and poor analgesic practices. Negative provider attitudes used in these studies have been linked to responses to questions about drug-seeking behaviors of patients, over-reporting of pain, and opinions that appearing comfortable while complaining of severe pain and requesting specific narcotic drug and dose are signs of drug-seeking behaviors.

It is important to note that the use of opioids is a first-line treatment for acute pain management for SCD patients and that adult patients have lived with SCD for years and are likely to be versed in pain management practices. For adolescent patients, the perception of
higher stigma has been associated with lower quality of life, less pain reduction in the hospital, and increased length of hospital stay.\textsuperscript{24}

\textbf{STATEMENT OF POSITION AND RECOMMENDATIONS}

The Student National Medical Association (SNMA) is the nation’s oldest and largest organization focused on the needs and concerns of medical students of color and has been strongly dedicated to addressing the needs of underserved communities since 1964. Sickle Cell Disease (SCD) is the most common inherited blood disorder in the United States affecting approximately 100,000 individuals. A large majority of these individuals come from African-American and Hispanic communities that at baseline are known to have disparities in rates of poverty, poor access to medical care, and poor quality of medical care which can be exacerbated by SCD, a disease that is strongly characterized by high utilization of the healthcare system. Thus, the SNMA has the following position and recommendations:

1. The SNMA supports continued legislation for the development and maintenance of a national program with the mission of supporting public health initiatives and funding for research programs focusing on SCD.
2. The SNMA supports the development of improved education and training programs for the treatment of SCD, especially in rural areas with lack of health care providers with expertise in caring for individuals living with SCD.
3. The SNMA recommends further efforts in addressing barriers to the engagement of people living with SCD in future research and clinical trials.
4. The SNMA supports future research and clinical trials for potentially curative therapies for SCD.
5. The SNMA recognizes the need for immediate attention to the opioid epidemic in the United States but is concerned for the implications for pain management for those living with SCD. Thus, the SNMA recommends further research into acute and chronic pain in patients with hematologic diseases and suggests an approach that improves the prescribing of opioids in a manner that reduces misuse yet acknowledges the need for opioids for acute and chronic pain treatment for individuals with clinical indications.
REFERENCES


