
Genetic Services Policy Project

Sickle Cell Disease: A Policy Brief

What is Sickle Cell Disease (SCD)?

- SCD is an autosomal recessive inherited disorder that affects red blood cells. It is one of several different hemoglobinopathies.
- SCD presents in varying degrees of severity with multi-system manifestations.

Who is affected by SCD?

- Approximately 72,000 children and adults suffer from SCD in the United States, with the highest prevalence in individuals with African ancestry.
- 1 in 500 African-American births and 1 in 1,000-1,400 Hispanic births are affected.
- An estimated 2 million people in the U.S, including 8% of African Americans, are carriers.

What are the genetic and non-genetic contributions to SCD?

- The genetic abnormality associated with SCD is a point mutation on the hemoglobin beta gene (HBB) on chromosome 11. This mutation leads to the production of an abnormal hemoglobin, referred to as Hb S.
- SCD results when an individual inherits two copies of the gene for hemoglobin S (Hb SS). The abnormal hemoglobin causes red blood cells to become deformed (“sickle shape”) when exposed to low oxygen, dehydration, or other stressors. Clusters of sickled cells block small blood vessels leading to pain and organ damage.
- SCD also encompasses disorders combining Hb S with another abnormal hemoglobin: hemoglobin C (Hb SC), sickle β -thalassemia (Hb S β ⁺-thalassemia and Hb S β ⁰-thalassemia), D-Punjab, and O-Arab.

What does it mean to be a carrier of sickle cell trait?

- Sickle cell carriers have one copy of Hb S, and are almost always asymptomatic.
- Rare cases of death have occurred in carriers in association with extreme exertion (e.g., athletes and military recruits). Otherwise, life expectancy for carriers is normal.
- Carrier frequency (Hb S) varies by ethnicity:
 - 1:14 in African Americans
 - 1:176 in Native Americans
 - 1:183 in Hispanics
 - 1:360 in Middle Eastern groups
 - 1:625 in Caucasians not of Middle Eastern origin
 - 1:1336 in Asians

What are the clinical features of SCD?

- Pain is a hallmark of SCD. Sickle cell crisis, or vaso-occlusion, is responsible for both acute (5-7 days) and chronic (weeks to months) pain syndromes.

- Other serious life-threatening complications include stroke, overwhelming infections with *Streptococcus pneumoniae* and *Hemophilus influenza*, splenic and hepatic sequestration crises, and aplastic anemia.
- Additional symptoms and signs include: swelling of the hands and feet, fatigue, respiratory symptoms, acute chest syndrome, and neurological changes due to occlusion of small blood vessels in the brain.
- With disease management, most individuals with SCD now live beyond 40 years of age.

What are the psychosocial impacts of SCD?

- SCD often has significant psychosocial impacts on individuals and families affected by the disease. Quality of life may be significantly impaired, particularly due to pain issues.
- Chronic pain syndromes and chronic illness behavior are major concerns, and may contribute to stigma associated with the disease.
- Cognitive difficulties and learning problems may follow neurologic events.
- Missed school and work, reliance on public assistance programs, and financial stress are common.
- Adolescents are at particularly increased risk of emotional distress and relationship difficulties.

Who provides care for SCD? In what setting?

- Multiple providers care for individuals with SCD and their families including primary care providers (e.g., pediatrics, family medicine), hematology specialists, genetic specialists, pain management specialists, high-risk obstetricians, and social workers. Pediatric hematologists are often the primary source of care.
- The National Heart, Lung and Blood Institute (NHLBI) at the National Institutes of Health supports 11 comprehensive sickle cell centers in urban areas with high concentrations of SCD patients. These centers have a clinical research focus.
- Additional sickle cell clinics are available at some large academic medical centers and children's hospitals.
- The American Academy of Pediatrics stresses the importance of the medical home concept for children with SCD.

What are standard treatments and therapies for SCD?

- Life-long comprehensive care is required to minimize morbidity and reduce early mortality.
- Some individuals require extensive therapies and hospitalization for the specific symptoms and complications of SCD.
- Daily penicillin prophylaxis is recommended for all children with SCD (newborn to age 5 years) to protect against life-threatening infections.
- Chronic transfusion therapy reduces the risk of stroke.
- Sickle cell pain crises are often managed with drug therapy, including narcotics.
- Coping mechanisms, adequate pain management, and cohesive family units help to prevent psychological instability and the development of a chronic pain syndrome.
- Hydroxyurea may reduce the frequency of severe pain, acute chest syndrome, and the need for blood transfusions in adults who respond to the drug. Long-term studies of hydroxyurea

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use demonstrate a 40% reduction in mortality. (Steinberg et al. 2003) Appropriate pediatric dosing is under investigation.

- Bone marrow transplantation with hemopoietic stem cells, ideally from an HLA matched sibling donor, may cure SCD, but only a limited number of patients with SCD are appropriate candidates for this treatment.
- Pregnancies in women with SCD are high risk and associated with increased morbidity and mortality.

What costs are associated with SCD?

- Charges for chronic transfusion for stroke prevention range from \$9,828 to \$50,852 per patient per year.
- In 2004, the average cost of hospitalization for SCD was \$6,223 with over 84,000 admissions. Total hospital costs for hospitalizations due to SCD equaled \$488 million.
- In the same year, there were 20,271 hospital discharges for children with sickle cell disease and vaso-occlusive crises with an average length of stay of 4.4 days.
- A large proportion of hospital costs are covered by public insurance, with 66 percent paid by Medicaid, 13 percent paid by Medicare, and only 15% covered by private insurance. (Steiner, Miller 2006)

What is the role of genetic services in SCD?

- Overview
 - The primary role of genetic services in SCD is in the identification of carriers and affected individuals, as well as counseling for reproductive decision-making. Genetic research plays an important role in understanding the disease and in the development of new therapies.
 - Population based screening programs in the 1970s failed to differentiate between carrier status and the presence of SCD, leading to confusion and discrimination against carriers.
 - Negative perceptions associated with historical events and stigma associated with the disease in a racially disadvantaged group may continue to influence utilization of genetic services in at-risk populations.
- Newborn screening
 - Newborn screening for hemoglobinopathies using isoelectric focusing and hemoglobin electrophoresis typically identifies individuals with SCD and may identify carriers. DNA analysis may be used for follow-up in some situations.
 - Currently, SCD and other hemoglobinopathies are included in all state newborn screening programs. New Hampshire recently added hemoglobinopathies to its mandatory screening panel (previously it was voluntary).
 - Newborn screening for SCD began in 1975, and was universally endorsed when studies demonstrated the life-saving benefits of penicillin prophylaxis in 1986.
 - While most states have a policy for notifying parents of carriers identified through newborn screening programs, these policies are not uniform and follow-up services (e.g., counseling) vary between states.
- Carrier screening and prenatal diagnosis
 - Carrier screening in the preconception or prenatal period may be used to identify

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carrier couples. Standard of care is to offer screening to individuals and couples based on racial/ethnic background.

- Prenatal diagnosis, through chorionic villus sampling or amniocentesis and subsequent DNA analysis, may follow positive carrier screening tests. Prenatal diagnosis may offer reassurance If the fetus is unaffected or give the couple the options of preparing for the birth of an affected child or terminating the pregnancy.
- Pre-implantation genetic diagnosis is possible for carrier couples who choose to undergo *in vitro* fertilization; however, this option is expensive and not widely utilized.
- Carrier screening of athletes
 - Recent consensus statements from the National Athletic Trainers Association and the American College of Pathology (2007) recommend pre-participation carrier screening of athletes and accommodations to prevent sudden death in association with heat and overexertion.
- Diagnosis
 - Specimens with abnormal newborn screening results are retested using a second, complementary electrophoretic technique, high performance liquid chromatography (HPLC), immunologic tests, or DNA-based assay to assess the beta hemoglobin gene.
 - Given universal newborn screening, diagnostic testing to evaluate a symptomatic child is now a rare occurrence, though it is possible as some parents choose to opt-out of newborn screening.
- Genetic counseling
 - Genetic counseling is recommended for carrier couples and families with a child diagnosed with SCD or identified as a SCD carrier on newborn screening.
 - Studies suggest low rates of utilization of genetic counseling services.
 - Several states have developed “sickle cell trait counselor” training programs to increase the availability of qualified counselors.
- Genetic treatment
 - Gene therapy
 - Stem cell transplantation
- Genetic research
 - Genetic determinants that may predict response to treatments, e.g. hydroxyurea. (Ma, et al. 2007)

What genetic services delivery or policy issues are highlighted in this case?

- Low utilization of genetic counseling and carrier screening by at-risk individuals and couples
 - Limited public awareness of SCD
 - Limited provider awareness/attention to carrier screening, especially in non-prenatal settings
 - High “single” parent/out-of-wedlock/teen birth rates in African American population (both members of couple may not be available for testing)
- Lack of access to high quality, comprehensive treatment services, particularly for adults

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- Limited number of providers with knowledge and experience managing SCD, especially adult providers
- Geographic limitations in comprehensive services
- Variability in use of effective treatment
- High reliance on emergency department for care
- Limited psychosocial support services
- Significant reliance on public programs/payers (i.e., Medicaid and Social Security Disability Insurance) by individuals with SCD
 - 65% of hospitalizations for SCD covered by Medicaid
 - Challenges for adults with SCD in maintaining jobs with health insurance benefits
 - Poor reimbursement by public programs may be a barrier to physicians taking on SCD patients, particularly adults
- Other issues
 - Cost, coverage, and reimbursement of emerging technology for treatment of SCD
 - Gaps in research funding support
 - Appropriate follow-up after identification of carriers via newborn screening programs/access to genetic counseling
 - Concern regarding sickle cell trait in athletes and risk of death from extreme exercise

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