Sickle Cell Disease

BACKGROUND

Sickle cell disease is a genetic disorder that affects the body’s red blood cells. In this disease, defective hemoglobin (a substance that carries oxygen in the blood) causes the red blood cells to change shape (into a sickle) when oxygen is released to tissues. Normal red blood cells are round and are able to move through small blood vessels in the body to deliver oxygen. In sickle cell disease, a chemical change in hemoglobin causes the substance to form long rods in the red blood cell as the hemoglobin releases oxygen. These rigid rods change the shape of the red blood cell into a sickle shape, hence the name of the disease.

Individuals with sickle cell disease may have hemoglobin "S", SC, S-beta thalassemia and others genetically distinct conditions, whereas others without this disease have hemoglobin "A". Sickle cell disease is found most often in African-Americans and Africans. However, other ethnic groups also can have sickle cell disease.

**Trait.** Sickle cell is a benign carrier condition, usually with none of the symptoms of sickle cell anemia. It is generally only a laboratory diagnosis in which one sickle cell gene has been inherited along with a normal gene.

**Population.** There are approximately 2.5 million people in the United States and 300 million in the world who have sickle cell trait. Everyone with sickle cell trait needs genetic counseling (not necessarily from a geneticist), regarding the risk of having a child with sickle cell disease.

**Presence, Geographic Coverage and Prevalence.** The presence of sickle cell trait appears to be protective against severe falciparum malaria, explaining the persistence of this gene in the world population. The gene for sickle cell anemia is widespread throughout the world, being present in Africa, Mediterranean countries (especially Greece), the Middle East, and parts of India. The prevalence of sickle cell trait is approximately 8 to 10 percent in African Americans and as high as 25 to 30 percent in certain areas of western Africa. The Hispanic population is also at risk for sickle cell disease. At least 1 in 180 Hispanic births have sickle cell trait.

Pathophysiology of Sickle Cell Disease

A chemical change in hemoglobin causes the substance to form long rods in the red blood cell as the hemoglobin releases oxygen. These rigid rods change the shape of the red blood cell into a sickle shape.

The sickle-shaped red blood cells break apart easily, causing anemia. Sickle red blood cells live only 10-20 days instead of the normal 120 days.

The damaged sickle red blood cells also clump together and stick to the walls of blood vessels, blocking blood flow.

Severe pain is an emergency called acute sickle cell crisis. A person may not know what brought on the pain, but infection and dehydration are common triggers.
INHERITENCE PATTERN OF SICKLE CELL DISEASE

A simple blood test is used to diagnose SCD and is often during routine newborn screening tests at the hospital; however, SCD can be diagnosed before birth. Early diagnosis and treatment is important as children with SCD are at an increased risk of infection and other health problems. Common types of SCD include:

- **HbSS** is the most severe form of SCD, occurring in those who inherit one sickle cell gene (‘S’) from each parent.
- **HbSC** is a milder form of SCD and is found in those who inherit a sickle cell gene (‘S’) from one parent and a gene for an abnormal hemoglobin called ‘C’ from the other parents.
- **HbS beta thalassemia** occurs when one inherit one sickle cell gene (‘S’) from one parent and one gene for beta thalassemia from the other parent. There are two types of beta thalassemia: ‘0’ and ‘+’. Individuals with HbS beta 0-thalassemia usually have a severe form of SCD; those with HbS beta + -thalassemia may have a milder form.
- **HbSD, HbSE, and HbSO** are rare types of SCD and are found in those who inherit one sickle cell gene (‘S’) and one gene from an abnormal type of hemoglobin (‘D’, ‘E’, or ‘O’).
- **HbAS** is found in individuals who have a sickle cell trait and inherit one sickle cell gene (‘S’) from one parent and one normal gene (‘A’) from the other parent. This is also known as sickle cell trait (SCT) – individuals with SCT usually do not have any of the signs of the disease and live a normal life, but can pass the trait on to their children.
  - If both parents have SCT, there is a 50% chance that any child of theirs also will have SCT. Such children will not have symptoms of SCD, but they can pass SCT on to their children.
  - If both parents have SCT, there is a 25% (or 1 in 4) chance that any child of theirs will have SCD. There is the same 25% (or 1 in 4) chance that the child will not have SCD or SCT.
  - If one parent has SCT, there is a 50% (or 1 in 2) chance that any child of this parent will have SCT and an equal 50% chance that the child will not have SCT.

FREQUENT SYMPTOMS OF SCD

Sickle cell disease is diagnosed by examining a sample of blood under a microscope. Confirming diagnosis is made by a hemoglobin electrophoresis, which is also the standard diagnostic test used in most state newborn screening tests. When the abnormal sickle-shaped cells in the blood are identified, a diagnosis is made.

This is the most common symptom of sickle cell disease. The sickle shape makes the cells stiff and sticky causing them to become stuck in the vessels, destroyed by the spleen, or simply die because of their abnormal function. Severe anemia can make a person pale and tired, and makes the person’s ability to carry oxygen to the tissues more difficult. Healing and normal growth and development may be delayed because of chronic anemia.

This occurs when the flow of blood is blocked to an area because the sickled cells have become stuck in the blood vessel. These are also called vaso-occlusive crises. The pain can occur anywhere, but most often occurs in the chest, arms, and legs. Painful swelling of the fingers and toes, called dactylitis, can occur in infants and children younger than age 3. This is often the first presenting sign in children not diagnosed on newborn screen. Priapism is a painful sickling that occurs in the penis. Any interruption in blood flow to the body can result in pain, swelling, and possible death of the surrounding tissue not receiving adequate blood and oxygen.

ACS occurs when sickling is in the chest, and it can be a life-threatening complication of sickle cell disease. It often occurs suddenly, when the body is under stress from infection, fever, or dehydration. The sickled cells stick together and block the flow of oxygen in the tiny vessels in the lungs. ACS resembles pneumonia and can include fever, pain, and a violent cough. It can quickly progress to respiratory failure if not treated promptly. Multiple episodes of acute chest syndrome can cause permanent lung damage and/or Congestive Heart Failure.
Crisis are a result of sickle cells pooling in the spleen. Sequestration can cause a sudden drop in hemoglobin and can be life-threatening if not treated promptly. The spleen can also become enlarged and painful from the increase in blood volume. After repeated episodes of splenic sequestration, the spleen becomes scarred, and permanently damaged. Most children, by age 8, do not have a functioning spleen either from surgical removal, or from repeated episodes of splenic sequestration. The risk of infection is a major concern of children without a functioning spleen. Infection is the major cause of death in children younger than age 5 in this population.

Stroke. This is another sudden and severe complication of children with sickle cell disease. The misshapen cells can block the major blood vessels that supply the brain with oxygen. Any interruption in the flow of blood and oxygen to the brain can result in devastating neurological impairment. Having had one stroke from sickle cell anemia, a child is more likely to have a second and third stroke.

Jaundice. Jaundice is a common sign and symptom of sickle disease and is characterized by yellowing of the skin, eyes, and oral mucosa. Sickle cells do not live as long as normal red blood cells and, therefore, they are dying more rapidly than the liver can filter them out. Bilirubin (which causes the yellow color) from these broken down cells builds up in the system causing jaundice. Priapism. An obstruction of the penis by sickle cells. If not promptly treated, it can result in impotence.

KEY MILESTONES OF SCD

The Key Milestones of Prevention for primary disease manifestations include:
- Hydroxyurea induces fetal Hgb production and makes cells less likely to sickle.
- Penicillin prophylaxis for all children under age 5 and anyone older who is surgically or functionally asplenic.
- Folic acid can create new blood cells and can be ingested via supplements or eating green, leafy vegetables.
- Proper immunizations and well-child care including specialty anticipatory guidance (specialist) about the disease.

The Key Milestones of Treatment for primary disease manifestations include:
- Drinking plenty of water daily (8 to 10 glasses) or receiving fluid intravenously (to prevent and treat pain crises).
- Transfusion when indicated - (for anemia, and to prevent stroke; transfusions are also used to dilute the HbS with normal hemoglobin to treat chronic pain, acute chest syndrome, splenic sequestration, and other emergencies).
- Pain medications including anti-inflammatories and opiates as necessary.
- Blood and bone marrow stem cell transplants may offer a cure for a small number of people. Transplants have been effective in curing or reducing symptoms in some children with sickle cell disease. The decision to undergo this procedure is based on the severity of the disease and the availability of a suitable bone marrow donor.

The Key Milestones to Prevent Complications of primary disease manifestations include:
- Preventive transfusion for those who have had a stroke or repeated ACS.
- Patients with sickle-cell disease (SCD) receiving chronic transfusions of red blood cells are at risk of developing transfusional iron overload over time. Transfusional iron overload is characterized by an increase of labile plasma iron (i.e., non-transferrin bound iron) in the body, which can lead to functional impairment in vital organs.
- Tricyclic antidepressants such as amitriptyline.
- Anticonvulsants such as Gabapentin.

BEHAVIORAL HEALTH AND PSYCHOSOCIAL FACTORS OF SCD

Children with sickle cell disease are 2 to 3 times more likely than their healthy peers to have mental health problems, a feature that is consistent with children with any chronic illness. In addition to an increase in mental health issues for the sickle cell child, nearly half of their mothers also reported significant symptoms of stress.

Hospitalization is an especially hard time for children with sickle cell disease and their parents. The school-aged child with sickle cell disease, on average, will miss 29 days of school per year due to hospitalizations and home recovery. This creates challenges for the child, parents, social workers and educators. Treatment planning should therefore also include education issues.
Financial support to these families frequently becomes necessary because of the economic hardship that often accompanies hospitalization. Because of medical leave related to the child’s school absence or hospitalization, many families experience employment-related issues.

Denial. Children with sickle cell anemia are well most of the time, but certain complications can occur which are very serious and sometimes fatal (cause death). It may be hard to believe that a healthy looking child has a life threatening disease, but this is true when a child has sickle cell anemia. Parents may initially show denial of their child’s condition, but as episodes recur, the denial will break down.

Anxiety, Depression and Other Symptoms. The most frequent psychological problems encountered include increased anxiety, depression, social withdrawal, aggression, poor relationships and poor school performance. High levels of parental anxiety, overprotection, excessive feelings of responsibility and guilt. Children with sickle cell disease are also at high risk for neurological complications including strokes and silent infarcts of the brain. When the brain is impacted there are usually impairments in verbal, performance, and IQ measures. These cognitive deficits may further affect the child’s ability to manage pain, stress, and following a treatment plan.

Addiction and Substance Abuse in Patients with Sickle Cell Disease. Sickle cell does not predispose to or provide absolute protection from drug addiction. Treatment of patients with drug addiction and a sickle cell syndrome poses a number of very difficult management problems.
1. Drug addiction compromises the ability to diagnose and treat complications in the disease.
2. Pain episodes are less responsive to therapy in drug tolerant patients.
3. Drug seeking behavior may mask symptoms of serious complications.
4. Regular use of opiates may make the health of sickle syndrome patients worse.

Motivational Interviewing should be incorporated in assessing the member’s readiness to address substance use behaviors. Sickle cell syndromes complicate the treatment of narcotic addiction. It is not realistic to expect these patients to achieve the goal of many drug treatment programs which is total narcotic free status. Pain episodes may require administration of opiate analgesics on an infrequent basis for a short period of time, even in the setting of know addiction. Some patients may have complications that cause chronic pain which will be unmanageable with non-opiates once the individual has become use to the relief obtained by regular opiate use for prolonged period of time.

This treatment plan forms a basis for a formal contract which defines the treatment plan, health care givers and patient responsibilities, treatment alternatives, and consequences of non-compliance. Although it is acknowledged that many patients in this addicted group do not want specific treatment for addiction, a positive, constructive approach is required to provide adequate comprehensive medical management of patients with sickle syndromes and iatrogenic drug addiction. Addiction in the sickle cell patient must be addressed with a positive and constructive approach. Principles established in the treatment of addiction are incorporated into an individual treatment plan that takes the individual’s strengths, problems, and needs into account.

COMPLICATIONS OF SCD

Symptoms of SCD vary and typically begin during the first year of life, approximately around 5 months of age. Treatment options are different for each person depending on the symptoms. The only cure for SCD is a bone marrow or stem cell transplant. Common complications include:1,3,4

- Hand-Foot Syndrome
- Pain “Episode” or “Crisis”
- Anemia
- Infection
- Acute Chest Syndrome
- Splenic Sequestration
- Vision Loss
- Leg Ulcers
- Stroke
- Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

Other possible complications of SCD include:
- Damage to body organs (like the liver, heart, or kidneys), tissues, or bones due to a lack of blood flow
- Malnutrition / growth retardation among adolescents can cause a delayed onset of puberty; infertility in males
• Gallstones
• Painful erection of the penis (priapism) can last ≤ 2 hours or ≥ 4 hours and may lead to impotence

LIVING WITH SCD

Providers can encourage parents and caregivers raising a child with SCD to keep in mind the following:

• Parents should discourage a "sick person" identity and instead, encourage regular lifestyle.
• No special diet is needed. Encourage a healthy balanced diet.
• Discipline should be administered the same as any other child.
• The importance of school work and a good education should be stressed.
• A regimen of regular follow up with the patient's medical team should be scheduled.
• It is important for the parent and child to know that there can be a delay as long as three years in reaching full adult development. The adolescent with sickle cell anemia may still look and feel like a child while his or her friends are developing adult characteristics. Reassurance that they too will grow up and mature will be necessary to relieve anxious feelings.

Sickle cell disease is a complex hereditary disease. Quality medical care takes a comprehensive team of doctors, nurses and health care professionals working together. Your doctor should have a thorough knowledge of sickle cell disease in order to help prevent serious problems with your health. Every person with sickle cell disease should have a hematologist and a primary care physician that knows the patient’s detailed medical history in order to provide the best medical care possible.

Maintaining a healthy lifestyle starts with preventing infections. Keep up to date on all vaccines including the flu vaccine, pneumococcal vaccine and any others recommended by a doctor. Take all medications, including penicillin, as prescribed by a doctor. Do not miss doses, and do not take more than recommended. Washing hands with soap and clean water is a simple and essential way to prevent infections.

It is critical that people with sickle cell disease stay hydrated at all times. Drinking 8 glasses of water each day is a good way to keep the body hydrated. Eating a balanced meal and making healthy choices are important for proper nutrition.

Certain uncooked foods can carry harmful bacteria. Be sure to wash anything that comes into contact with contaminated food including hands, cutting boards, knives, counters, or any other utensil. Wash all fruits and vegetables before eating them and cook meat until it’s well done.

Maintaining a balanced body temperature is very important, getting too hot or too cold can cause sickness. Be sure to wear layers to adapt to changing temperatures.

The harmful bacteria Salmonella is present in some reptiles and is especially harmful to people with sickle cell disease. Children and adults should stay away from snakes, lizards and turtles.

In general, people who have sickle cell disease have a reduced life expectancy. Some people with the disease can remain without symptoms for years, while others do not survive beyond infancy or early childhood. New treatments for sickle cell disease are improving life expectancy and quality of life. People with sickle cell disease can survive beyond their 50s with optimal management of the disease.

MANAGING PREGNANCY AND SCD

The risks for pregnancy depend on whether the mother has sickle cell disease or sickle cell trait. Generally, women with sickle cell trait are not at increased risk for problems, however, they may experience frequent urinary tract infections. During pregnancy sickling and anemia may result in lower amounts of oxygen going to the fetus and slowed fetal growth. Because sickling affects so many organs and body systems, women with the disease are more likely to have complications in pregnancy. Complications and increased risks for the mother may include, but are not limited to:

• Infection, including the urinary tract (especially kidney) and lungs.
SICKLE CELL DISEASE
HS-1038

- Gallbladder problems including gallstones.
- Heart enlargement and heart failure from anemia.

Complications and increased risks for the fetus may include, but are not limited to, the following:
- Miscarriage
- Intrauterine growth restriction (poor fetal growth)
- Preterm birth (before 37 weeks of pregnancy)
- Low birth weight (less than 5.5 pounds)
- Stillbirth and newborn death

Testing of the baby's father is recommended prior to pregnancy, or at the first prenatal visit. If the baby's father has sickle cell trait, amniocentesis (a procedure used to obtain a small sample of the amniotic fluid) or other methods of prenatal diagnosis may be offered to help determine if the fetus has the trait or the disease.

Early and regular prenatal care is important for pregnant women with sickle cell disease. More frequent prenatal visits allow for close monitoring of the disease and of fetal well-being. General pregnancy care includes a healthy diet, prenatal vitamins, folic acid supplements (a B vitamin), and preventing dehydration.

Some women may benefit from blood transfusions to replace the sickled cells with fresh blood. These may be done several times during the pregnancy to help increase the blood's ability to carry oxygen and decrease the number of sickled cells. It is important for women who receive blood transfusions to be screened for antibodies that may have been transferred in the blood and that may affect her fetus. The most common antibodies are to the blood factor Rh.

Fetal testing may begin in the second trimester and include:
- Ultrasound: A test that uses sound waves to measure fetal growth.
- Non-stress test: This test measures fetal heart rate in response to fetal movement.
- Biophysical profile: This test combines an ultrasound with the non-stress test
- Doppler flow studies: This is a type of ultrasound which uses sound waves to measure blood flow.

During labor, intravenous (IV) fluids are given to help prevent dehydration. Most women will receive extra oxygen through a mask during labor and a fetal heart rate monitor is often used to watch for changes in heart rate and signs of fetal distress. There are no special recommendations for the type of delivery for women with sickle cell disease and most women can deliver vaginally, unless there are other complications. In addition, the U.S. Preventive Services Task Force (USPSTF) (2007) recommends screening for sickle cell disease in newborns (Grade: A Recommendation).

SPECIAL CONSIDERATIONS FOR PEDIATRIC MEMBERS

In 2011, the American Academy of Pediatrics reaffirmed their 2002 guideline. Health maintenance for pediatric members should be comprehensive, ensuring that providers discuss the following with the member and/or caregiver: prophylactic medications, immunizations, comprehensive medical evaluation and psychosocial care. Further, the AAP recommends that health supervision should consist of family education, health maintenance, acute illness and psychosocial care. A detailed overview of the recommendations can be found at http://pediatrics.aappublications.org/content/109/3/526.full.

MEMBER EDUCATION

Individuals with SCD have less access to comprehensive team care than people with genetic disorders such as hemophilia and cystic fibrosis. It is important for providers to talk to members with SCD, emphasizing that one can live a full life and enjoy most activities that other people do. Providers shall educate members of the following:

Regular health checkups with a primary care physician (PCP) may prevent serious complications of the disease:
- Babies from birth to 1 year of age should see a doctor every 2 to 3 months
- Children from 1 to 2 years of age should see a doctor at least every 3 months
- Children and adults from 2 years of age or older should see a doctor at least once every year
Infection Prevention should be stressed to members as common illnesses like the flu can be dangerous for someone with SCD. They should limit exposure to family or friends who may be sick as well as practice good hand washing when cooking or eating food. In addition, hand washing should occur upon one:

- Blowing their nose, coughing, or sneezing
- Shaking hands
- Touching people or things that can carry germs (e.g., diapers or toilets, raw meat and eggs, unwashed vegetables, animals, animal waste, trash or a sick person)

Emergency Treatment should be discussed with members. Providers can instruct individuals with SCD to proceed to an emergency room or urgent care facility when any of the following occur:

- Fever above 101°F
- Difficulty breathing
- Chest pain
- Abdominal (belly) swelling
- Severe headache
- Sudden weakness or loss of feeling and movement
- Seizure
- Painful erection of the penis that lasts more than 4 hours
- Pain anywhere in the body that will not go away with treatment at home
- Any sudden problem with vision

Food Safety is important to reduce the chance of bacteria (salmonella) being ingested. Members should be mindful of the following when cooking and eating:

- Wash hands, cutting boards, counters, knives, and other utensils after they touch uncooked foods
- Wash vegetables and fruit well before eating them
- Cook meat until it's well done. The juices should run clear and there should be no pink inside
- Do not eat raw or undercooked eggs; be mindful of things raw eggs might be in (e.g., sauces, cookie dough)
- Do not eat raw or unpasteurized milk or other dairy products; labels should say “pasteurized”

Reptiles may also transmit salmonella; children should limit or eliminate exposure to turtles, snakes, and lizards.

Acetaminophen Use. In August 1, 2013, the U.S. Food and Drug Administration (FDA) notified healthcare professionals and patients that acetaminophen has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal. Reactions can occur with first-time use of acetaminophen or at any time while it is being taken. Other drugs used to treat fever and pain/body aches (e.g., non-steroidal anti-inflammatory drugs, or NSAIDS, such as ibuprofen and naproxen) also carry the risk of causing serious skin reactions.

Vaccines can prevent many infections in children with SCD. Members benefit from regularly scheduled vaccines and the:

- Flu vaccine (influenza vaccine) every year after 6 months of age
- A special pneumococcal vaccine (called 23-valent pneumococcal vaccine) at 2 and 5 years of age
- Pneumococcal conjugate vaccine (PCV13) between 6-18 years of age, if not previously received the vaccine
- Meningococcal vaccine, if recommended by a doctor

NOTE: Adults should receive the flu vaccine every year, as well as the pneumococcal vaccine and any others recommended by a doctor.

Penicillin use is also an option for individuals with SCD. Penicillin (or other antibiotic prescribed by a doctor) may be used in children every day until at least 5 years of age.

Providers can direct members to the following Centers for Disease Control and Prevention resources:

- [http://www.cdc.gov/ncbddd/sicklecell/freematerials.html](http://www.cdc.gov/ncbddd/sicklecell/freematerials.html)
HEDIS AND STAR MEASURES

NCQA and CMS have not published measures for topic.

REFERENCES


LEGAL DISCLAIMER

Clinical Practice Guidelines made available by WellCare are informational in nature and are not a substitute for the professional medical judgment of treating physicians or other health care practitioners. These guidelines are based on information available at the time and may not be updated with the most current information available at subsequent times. Individuals should consult with their physician(s) regarding the appropriateness of care or treatment options to meet their specific needs or medical condition. Disclosure of clinical practice guidelines is not a guarantee of coverage. Members of WellCare health plans should consult their individual coverage documents for information regarding covered benefits. WellCare does not offer medical advice or provide medical care, and therefore cannot guarantee any results or outcomes. WellCare does not warrant or guarantee, and shall not be liable for any deficiencies in the information contained herein or for any inaccuracies or recommendations made by independent third parties from whom any of the information contained herein was obtained. Note: The lines of business (LOB) are subject to change without notice; consult www.wellcare.com/Providers/CPGs for list of current LOBs.

Easy Choice Health Plan ~ Harmony Health Plan of Illinois, Inc. ~ Missouri Care, Inc. ~ ‘Ohana Health Plan, a plan offered by WellCare Health Insurance of Arizona, Inc. ~ WellCare Health Insurance of Illinois, Inc. ~ WellCare Health Plans of New Jersey, Inc. ~ WellCare Health Insurance of Arizona, Inc. ~ WellCare of Florida, Inc. ~ WellCare of Connecticut, Inc. ~ WellCare of Georgia, Inc. ~ WellCare of Kentucky, Inc. ~ WellCare of Louisiana, Inc. ~ WellCare of New York, Inc. ~ WellCare of South Carolina, Inc. ~ WellCare of Texas, Inc. ~ WellCare Prescription Insurance, Inc. ~ Windsor Health Plan ~ Windsor Rx Medicare Prescription Drug Plan

MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>History and Revisions by the Medical Policy Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/5/2015</td>
<td>Approved by MPC. Inclusion of Care Management items.</td>
</tr>
</tbody>
</table>