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A Handbook for Families

Sickle Cell Disease

HEMATOLOGY SERIES

Sickle Cell Disease

A HANDBOOK FOR FAMILIES

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WHAT IS SICKLE CELL DISEASE?

Sickle cell disease is an inherited blood disorder that affects the ability of red blood cells to carry oxygen throughout the body. Normally, red blood cells are round and flexible. Sickle cell disease causes red blood cells to change into a curved, or sickle, shape. These sickle-shaped red blood cells stick together, blocking blood flow to the hands, feet, joints, bones, and major organs. When blood flow to these areas decreases, the tissues do not get enough oxygen, causing pain and other problems. To understand how sickle cell disease affects the body, it helps to understand a little more about blood.

WHAT IS BLOOD?

Blood is a mixture of cells, proteins, and a watery substance called plasma. The cells in blood are made in our bone marrow, the sponge-like center of the bones in our skull, spine, pelvis, and ribs. Like water being pumped through a hose, our blood is pumped by our heart through small tubes called blood vessels. There are two types of blood vessels: arteries and veins. The arteries carry blood away from the heart and bring oxygen to the body's tissues. After delivering the oxygen to the tissues, the blood is returned to the heart through the veins.

Blood has many functions. It carries nutrients and gases throughout the body and carries waste away from the tissues and organs. Blood also helps fight infections and heal wounds.

Blood has four major components:

- White blood cells are the fighter cells, known as leukocytes. White blood cells, which are part of the immune system, protect the body from infection and disease.
- Platelets help stop bleeding. Platelets form a scab after skin or tissue has been injured.
- Red blood cells make up most of the cells in our blood. These small cells, known as erythrocytes, are slightly flattened, so they look like a doughnut with the hole filled in. The function of red blood cells is to carry oxygen, carbon dioxide, and nutrients throughout the body. Red blood cells contain a protein called hemoglobin, which carries oxygen throughout the body. The cells of the tissues use the oxygen and create carbon dioxide, a waste product. After red blood cells drop off oxygen at the tissues, they pick up carbon dioxide and carry it back to the lungs to be exhaled from the body.
- Plasma is a yellowish liquid consisting mostly of water. Plasma acts as a river, helping the white blood cells, red blood cells, and platelets flow freely through the blood vessels.

HOW DOES SICKLE CELL DISEASE AFFECT THE BLOOD?

Red blood cells normally contain hemoglobin A, also called adult hemoglobin. A child who has sickle cell disease has inherited an abnormal gene (called a gene mutation) for the production of hemoglobin. This gene mutation causes the body to make hemoglobin S, or sickle hemoglobin, instead of hemoglobin A. Sickle hemoglobin is not efficient at carrying oxygen. Under certain stressful conditions, such as fever and dehydration, the red blood cells change into a rigid sickle shape, like a crescent moon. When this happens, the sickle-shaped cells stick to each other and to the blood vessel walls instead of flowing easily through the vessels like soft, round, normal blood cells. When these sickle-shaped cells stick together, they block the flow of blood through the vessel and prevent the tissues from getting fresh, oxygenated blood. This is what causes pain, the most well-known symptom of sickle cell disease. However, this lack of oxygen also is responsible for many other problems, which will be addressed later.

People who do not have sickle cell disease make red blood cells that contain hemoglobin A. These red blood cells can live for almost 120 days. People with sickle cell disease make red blood cells that contain hemoglobin S. These red blood cells can sickle and on average live for only 10–20 days before breaking apart. This breaking apart of red blood cells is called *hemolysis*. It is hard for the body to replace the red blood cells fast enough, which causes anemia, a low hemoglobin level in people living with sickle cell disease. *Anemia* is the medical term for a low hemoglobin level. Anemia causes people to feel tired and weak, and severe anemia may require a blood transfusion.

WHO GETS SICKLE CELL DISEASE?

Sickle cell disease is a genetic disorder, meaning that a child can inherit the disease from parents who carry the gene mutation for sickle cell disease. Many people associate sickle cell disease with Africans and people of African descent. Although it is extremely common in Africa, sickle cell disease actually began in four areas of the world with a high incidence of malaria: Africa, India, the Mediterranean, and the Middle East. It is believed that the sickle cell mutation developed as a way to protect people living in these areas from malaria. (Malaria is a blood disease transmitted to humans by certain mosquitoes.) Today, there are people with sickle cell disease living in almost every country.

HOW IS SICKLE CELL DISEASE INHERITED?

Sickle cell disease is inherited in the same way that many of our genetic traits are inherited from our parents. Sickle cell disease is a recessive condition that occurs when a child inherits the sickle cell gene from both parents, one from the mother and one from the father. If a child only

inherits one sickle cell gene—from either parent but not both—he or she will have sickle cell trait and be referred to as a *carrier*. People who live with sickle cell trait do not experience the symptoms or problems experienced by those who live with sickle cell disease.

When parents who both have the trait have a pregnancy together, there is a one in four (25%) chance the child will have sickle cell disease, a two in four (50%) chance the child will have sickle cell trait, and a one in four (25%) chance the child will have normal hemoglobin chains (no disease or trait). The chances are the same with each pregnancy, so it is possible to have more than one child with sickle cell disease.

WHAT ARE THE TYPES OF SICKLE CELL DISEASE?

Although there are many types of sickle cell disease, four types are most common: sickle cell anemia (HbSS), sickle hemoglobin C (HbSC), sickle beta-zero thalassemia (HbS-ß0 thal), and sickle beta-plus thalassemia (HbS-ß+ thal).

Sickle Cell Anemia

Sickle cell anemia, also known as Hemoglobin SS (HbSS), is the most common and severe form of sickle cell disease. In this form, each parent passes on the mutated gene for sickle-shaped cells (hemoglobin S). As a result, the body only produces the abnormal sickle hemoglobin.

Sickle Hemoglobin C (HbSC)

Hemoglobin C is abnormal hemoglobin caused by another gene mutation. If one parent passes along a mutated hemoglobin S gene, and the other passes along a mutated hemoglobin C gene, the child is diagnosed with hemoglobin SC, or HbSC. Hemoglobin C (Hb C) is not concerning unless it is matched with HbS. Patients with HbSC tend to experience milder symptoms than those diagnosed with HbSS. However, severity varies from patient to patient, and some patients may experience the same severe symptoms as those with HbSS.

Sickle Beta Thalassemia

Beta (ß) thalassemia is another inherited disorder that affects the amount and quality of hemoglobin made by the body. The combination of the beta thalassemia gene with the sickle cell gene leads to a diagnosis of sickle beta thalassemia, which is a form of sickle cell disease. Sickle beta-zero thalassemia (HbS-ß0 thal) means there is no normal hemoglobin being made by the body. It usually is a serious form of sickle cell disease. Sickle beta-plus thalassemia (HbS-ß+ thal) means normal hemoglobin is being made but only in a small amount. This usually is a milder form of sickle cell disease, although severity varies from person to person.

WHAT ARE THE COMPLICATIONS OF SICKLE CELL DISEASE?

Because sickle cell disease affects blood, and blood travels to every part of the body, problems can occur almost anywhere in the body. The problems caused by sickle cell disease are a result of the damage caused by the sickle-shaped red blood cells and the chronic anemia caused by hemolysis. These problems can be *acute*, which means they have a rapid onset and are immediately obvious, or they can be *chronic*, which means they occur over time and are more subtle.

Acute Complications

Infection and Fever

People with sickle cell disease are at an increased risk for life-threatening infections. Sickle-shaped red blood cells can damage the spleen early in life. The spleen is an organ that helps to filter bacteria from the bloodstream and produces some white blood cells. The damaged spleen is no longer able to filter bacteria out of the blood. As a result, bacteria can travel through the blood and, in just a few hours, cause an overwhelming infection. These infections can cause shock and even death. Because of this, every time a person with sickle cell disease has a fever, it must be considered an emergency. You must contact a healthcare provider and seek medical attention immediately if your child has a fever. Your child will need laboratory work, including a blood culture and, possibly, a chest X ray. Your child will be given antibiotics either intravenously or by injection. Your child may be hospitalized or receive antibiotics in the clinic or emergency department.

It is impossible to know just by looking at your child whether their fever is caused by serious infection from bacteria or by another, less serious reason. However, bacteria can quickly and severely affect the body, which is why it must be assumed that the fever is caused by bacteria, and there should be no delay in seeking treatment. It is important to have a thermometer to check your child's temperature. You must seek immediate medical attention for your child for any temperature greater than 101 °F or 38.3 °C.

Splenic Sequestration

Oxygen levels in the spleen are low, and the blood moves through it slowly. Because of this, red blood cells tend to sickle in the spleen. In some cases, this can result in a blockage of blood flow out of the spleen, and red blood cells and platelets can become trapped. Normally, the spleen is tucked under the left side of the rib cage. When blood becomes trapped, the spleen swells and there is a rapid fall in hemoglobin and platelets as the amount of blood circulating in the rest of the body decreases. This condition is known as *splenic sequestration* and is a medical emergency.

Sequestration is most common in children with HbSS and HbS-ß0 thal. It can occur in the less severe diseases of HbSC and HbS-ß+ thal. Your child's hematology team will show you how to recognize a swollen spleen. Your child may appear pale, have decreased energy, or complain of abdominal pain when their spleen becomes larger than normal. Often, splenic sequestration will happen repeatedly. Your child may need their spleen to be removed surgically in an operation called a splenectomy. If this is the case, your hematology team will discuss the risks and benefits a splenectomy.

Pain Crisis (Vaso-Occlusive Crisis)

Under certain conditions—such as exposure to extreme temperatures, fever, dehydration, infection, or stress—red blood cells can become sickle shaped in people who have sickle cell disease. This may block the blood vessels, preventing oxygenated blood from getting to the body's tissues. This lack of oxygen can be very painful. Damage to the blood vessels and swelling in the area of the blockage can increase pain. Dactylitis, or hand and foot syndrome, often is the first type of sickle-cell related pain experienced by babies and toddlers with sickle cell disease. *Dactylitis* is swelling and extreme tenderness in the hands, feet, or both. Pain not attributed to an injury (for example, a sprain, broken bone, or constipation) should be evaluated and treated as a pain crisis. Older children and adolescents will mainly experience pain in their long bones (arms and legs), chest, and back. Your child's healthcare provider will prescribe pain medications and give instructions for their administration. However, there will be times when home treatment is not enough to relieve the pain. In these cases, admission to the hospital or a trip to the emergency room or clinic may be necessary. This is discussed more in Pain Medication section.

Acute Chest Syndrome

Acute chest syndrome is a very serious complication of sickle cell disease and is the second most common reason those with sickle cell disease are hospitalized. Acute chest syndrome is the result of sickle-shaped red blood cells blocking the tiny vessels of the lungs. It is characterized by chest pain, difficulty breathing, fever, and changes to the lungs as seen on an X ray. Acute chest syndrome may be caused by pneumonia. A pain crisis may lead to acute chest syndrome, because pain can make it more difficult to expand the lungs and take deep breaths. Pain medications can make a child drowsy, which also interferes with taking deep breaths. For this reason, you and your child will be taught deep-breathing exercises, called *incentive spirometry*, to be used during a pain crisis to help prevent or treat acute chest syndrome.

Often, individuals experiencing acute chest syndrome will need a red blood cell transfusion. Given early, a transfusion may prevent transfer to an intensive care unit or the need to use a ventilator.

Aplastic Crisis

If your child develops signs of worsening anemia, such as fatigue (extreme tiredness), severe headache, or extremely pale lips and nail beds, your hematologist may suspect an *aplastic crisis* (a decrease in red blood cell production). An aplastic crisis has various causes, including parvovirus. Parvovirus B19 infection, known as "fifth disease," is a very common childhood infection that causes mild fever, cold symptoms, and a rash on the cheeks and other body parts. Parvovirus B19 infection can shut down the production of red blood cells in the bone marrow for up to 10 days. For most children,

this does not cause any serious problems. However, the red blood cells of children with sickle cell disease live only a short time, so parvovirus B19 infection can result in severe anemia (a decrease in hemoglobin). Because the bone marrow has stopped producing red blood cells, there are few young red blood cells.

Stroke

Over time, sickle cell disease may damage the blood vessels of the brain, making them narrower. Sickle-shaped red blood cells can block these damaged vessels and prevent oxygen from getting to the brain tissue, causing a stroke, which can result in permanent brain damage. A child who is having a stroke may have any of these symptoms: severe headache, weakness on one side, inability to speak or understand language, seizures, weakness in facial muscles (this makes one side of the face appear to droop or sag), change in vision, and trouble swallowing. A child may have a transient ischemic attack (TIA), which is like a stroke but with symptoms lasting less than 24 hours. If you suspect your child is having a stroke or TIA, seek immediate medical attention. The sooner medical treatment begins, the less damage the stroke can cause.

Approximately 10% of children with HbSS and HbS-ß0 thal are at risk of suffering a serious neurological event (stroke). The average age for experiencing such an event is 8 years old. A child who has suffered one stroke or TIA has an extremely high risk of having another, possibly more serious, stroke or TIA. For this reason, regular red blood cell transfusions are started. The goal of regular red blood cell transfusions is to replace the child's blood, which can sickle and cause further blockages, with non-sickled red blood cells (Hemoglobin A) from a donor.

Transcranial Doppler (TCD) imaging is now used routinely as a screening tool to determine if a child is at risk for stroke. TCDs detect abnormal flow through vessels of the brain that have suffered damage from sickle-shaped red blood cells. An abnormal TCD result is a strong predictor of an increased risk of stroke. Children found to have this should be offered regular transfusions. Annual screening with TCD should begin at 2 years of age for children with HbSS and HbS-ß0 thal.

Priapism

Sickle-shaped red blood cells can block the blood from flowing out of the penis. The result is *priapism*, a long-lasting and unwanted erection of the penis that often is extremely painful. Priapism is a medical emergency, especially if it lasts more than 2 hours. It is important that caregivers and health professionals instruct boys to let someone know when they are experiencing priapism. If not treated, priapism may lead to an inability to have a normal erection in the future. Priapism treatments vary but may include intravenous fluids and pain medication. Sometimes blood transfusions and medications that open up blood vessels are needed. If these measures do not work, a surgeon trained in this field, known as a urologist, will use a surgical procedure to release the trapped blood. It is common for priapism to happen again. Preventive measures, such as taking hydroxyurea and medications that dilate, or open, blood vessels may need to be used on a daily basis. Other preventative home measures include drinking plenty of water, taking a warm shower or bath, and taking pain medications.

Chronic Complications

Eye Problems

Bilirubin is a yellow substance found inside red blood cells. Because sickle-shaped red blood cells are fragile, they can break open easily and release bilirubin into the bloodstream, causing a yellow tint to the eyes that often is seen in people with sickle cell disease.

The retina is the thin lining on the inside of the eye that receives images the eye sees and changes them into messages the brain can read. The blood vessels of the retina are extremely tiny. Over time, the small blood vessels of the retina can become blocked by sickle-shaped red blood cells. To help the blood flow, the body creates new blood vessels to carry blood to the retina. However, these new vessels are weak and tend to break open, causing bleeding and damage to the retina, which is called *sickle cell retinopathy*. Sickle cell retinopathy has no symptoms in its early stages, which is when it is most easily treated by laser surgery. For this reason, children who have sickle cell disease should have yearly eye exams, beginning in kindergarten. Sickle cell retinopathy is most common in people with HbSC and in older adolescents and adults.

Heart and Lung Complications

The heart is a muscle. Its job is to pump blood to the lungs, which is where the blood picks up oxygen and carries it to all the tissues in the body. Because people with sickle cell disease have lower hemoglobin levels (anemia) and less oxygenated blood, their hearts must work harder. As a result, it is very common for them to have *cardiomegaly*, which is an enlarged heart. Individuals with sickle cell disease often are told that their hearts have a *murmur*, or unusual sound. These murmurs are most often the result of chronic anemia.

Children with sickle cell disease can develop a condition known as *pulmonary hypertension*, once thought to only affect adults with sickle cell disease. Pulmonary hypertension is high blood pressure in the artery that supplies blood to the lung from the heart. Pressure builds up as this artery becomes damaged by sickle-shaped red blood cells and becomes narrower. This increased pressure makes the heart's job much more difficult. The right side of the heart, which is the side that pumps blood into the lungs, can become enlarged and weak. When this happens, patients can experience shortness of breath and dizziness. These symptoms often are not felt until pulmonary hypertension has progressed. Fortunately, pulmonary hypertension can be detected early by a simple test called an *echocardiogram*. A visit to a heart specialist (cardiologist) may be needed to check for pulmonary hypertension in children and adults who have sickle cell disease.

Conditions that affect the lungs and the amount of oxygen that comes into the body, such as asthma and sleep apnea, must be controlled in a person living with sickle cell disease to decrease long-term problems. If your child is diagnosed with one of these conditions, it is very important that he or she is under the care of the appropriate specialist (pulmonologist) and that all of the treatment advice is followed.

Kidney Problems

The main job of the kidneys is to filter waste out of the blood. More than 1 million tiny filters inside the kidneys, called *nephrons*, remove the waste. The collected waste combines with water, which also is filtered by the kidneys, to make urine. The urine leaves the kidneys and travels down the ureters into the bladder. When the bladder is full enough, the pressure causes a person to feel the need to go to the bathroom. Urine then leaves the body through the urethra.

Sickle-shaped red blood cells can block the tiny vessels of the kidneys and damage the nephrons, causing the urine to be less concentrated than it should be. This results in an increased amount of urine and makes it very easy to become dehydrated. It also is the reason many children with sickle cell disease experience bed-wetting, known as *nocturnal enuresis*. These children can be treated the same as children who wet the bed and do not have sickle cell disease. Treatment for bed-wetting includes limiting fluids in the evening, using bed-wetting alarms, and, in some cases, taking medications.

If the nephrons continue to be damaged by sickle cell disease, the kidneys may lose their ability to filter the blood. In the worst-case situations, kidney failure may occur.

Kidney damage can be detected early with a simple urine test. The test checks the urine for a protein that the should have removed and for blood (hematuria). Urine sampled first thing in the morning gives the best indication of the kidneys' health. A kidney specialist (nephrologist) may be consulted if there is blood or protein in the urine.

Gallbladder Problems

The gallbladder is an organ in the digestive system that stores bile, which is needed to help digest fats. Bile is made from bilirubin, a substance contained in red blood cells. When red blood cells break open, the bilirubin is released into the bloodstream. Because people with sickle cell disease have a high rate of hemolysis, they have excess bile that can cause gallstones to form in the gallbladder. Gallstones may cause sharp, sudden pains in the upper-right abdomen, which may worsen after eating fatty or spicy foods. These stones are diagnosed by an abdominal ultrasound. Sometimes the gallbladder can become inflamed, resulting in fever, pain, or both. When this happens, the gallbladder may need to be surgically removed. Eating a diet low in fat may make the attacks less painful.

Joint Complications

The blood supply to the body's joints is limited. This is especially the case in ball-and-socket joints like those in the shoulders and hips. *Avascular necrosis* is a death of bone tissue that occurs in these joints after the blood flow is repeatedly blocked by sickle-shaped red blood cells. The femoral head, located at the top of the thigh bone, or femur, is at greatest risk for this problem. Avascular necrosis feels like arthritis pain, with stiffness and achiness, especially in the morning or after sitting for a while. If a child is still growing, physical therapy can be very helpful in healing the joint. For people who have finished growing, physical therapy can help relieve the pain and possibly delay the need for surgery. In some cases, joint-replacement surgery is needed.

Learning Issues

Children living with sickle cell disease may have brain damage that goes undetected. This damage can include narrowing of the blood vessels that supply the brain with blood or even silent strokes. Silent strokes are strokes that cause no physical symptoms but can be seen on a magnetic resonance imaging (MRI) scan or computed tomography (CT) scan of the brain. Also, like children who live with other chronic illnesses, children with sickle cell disease may miss many days of school and have days when they are not at their best. This can lead to learning challenges. It is recommended that children with sickle cell disease periodically undergo neuropsychological testing, a type of evaluation that determines a child's strengths and weaknesses in learning. It is important to let your child's doctor know if they are having learning challenges in school.

Growth and Development Delays

Ongoing anemia or chronic anemia (low hemoglobin) and high calorie needs may cause children with sickle cell disease to experience delayed growth. These children also may experience the changes of puberty at an older age than children who do not have sickle cell disease. Your child's healthcare team will weigh and measure your child regularly. If your child does not have any signs of puberty when expected or begins to fall behind the growth curve, they may refer your child to a growth and hormones specialist (endocrinologist).

Skin Complications

Leg ulcers are poorly healing skin sores typically found on the lower leg. They can occur in 10%–15% of older teen and adult patients who have sickle cell disease, usually those with HbSS or HbS-ß0 thal. These ulcers are the result of poor blood flow and usually develop following an injury to the skin. Leg ulcers are very difficult to treat, but many methods used to treat ulcers associated with other health conditions, such as diabetes, often are used to treat ulcers associated with sickle cell disease. In many cases, regular transfusions of red blood cells are given to increase the hemoglobin, dilute the sickle cells, and promote healing. It is important to pay special attention to any changes to or breaks in the skin before they become ulcers and to make your healthcare providers aware of any poorly healing wounds, especially on the legs.

Pregnancy Considerations

A woman with sickle cell disease can get pregnant. However, it is common for the disease and its complications to become more severe during pregnancy, as it is a stressful time for a woman's body. There may be risks to the developing baby, as well. Pregnancy in a woman living with sickle cell disease is considered high risk and must be closely monitored by both a high-risk pregnancy specialist and a hematologist.

Iron Overload

The body needs iron to make hemoglobin. Breakdown of red blood cells (hemolysis) results in the release of iron into the body so that it may be used to make new red blood cells. There is an increased rate of hemolysis in individuals living with sickle cell disease. Blood transfusions also can contribute additional iron to the body. Your child's hematology team will monitor the results of a laboratory test (called a *ferritin* test, which is also the name of the protein containing the iron) to determine if iron levels are becoming too high. The body has no way of getting rid of iron naturally. If the ferritin level is very high, medications called iron chelators may be used to remove excess iron from the body to prevent organ damage.

WHEN WILL MY CHILD NEED TO BE IN THE HOSPITAL?

From time to time, children diagnosed with sickle cell disease will need to spend time in the hospital. The most common reasons for hospitalization are fever and pain that cannot be relieved by medications at home. Other reasons include aplastic crisis, splenic sequestration, and respiratory symptoms.

Some children with sickle cell disease may need surgery. Because of chronic anemia and the potential for red blood cells to become sickle shaped, these children are at greater risk for complications from surgery and anesthesia. These complications include infection, acute chest syndrome, and stroke. Before surgery can take place, children often will need to receive fluid by vein and possibly a blood transfusion. Following surgery, they will need to be observed closely for complications. Make sure your child's hematology team is aware of any planned surgeries. This includes any time your child's dentist plans to use sedation or anesthesia.

WHAT TESTS AND PROCEDURES WILL MY CHILD NEED?

Blood Tests

Often, it will be necessary for your child to have blood tests to monitor their sickle cell disease, look for complications, and check responses to treatment. The following are some common blood tests:

- Hemoglobin electrophoresis measures the types of hemoglobin present in the blood to determine if your child has sickle cell disease and, if so, which type.
- A complete blood count (CBC) determines the number of white blood cells (infection-fighting cells) and platelets (clot-forming cells) and the level of hemoglobin in your child's body. A reticulocyte count, which measures the rate at which the body is producing new red blood cells, often is done with a CBC.
- A chemistry panel checks that your child's body has the correct amount of important substances such as electrolytes, protein, and sugar. It also checks the liver and kidney function and nutritional status.

- Blood cultures are observed in the lab for bacteria growth. Blood for these cultures will be drawn each time your child has a fever.
- ABO typing (blood type) and antibody screen tests help identify the compatible donor blood for your child in case a blood transfusion is needed.

Urine Tests

At times, your child will be asked to give a urine sample. This provides information about the health of the kidneys and whether there might be an infection in the urinary tract.

Radiology Tests

Radiology tests are used to detect changes that may indicate a future problem, diagnose a complication, or monitor your child's response to a treatment plan. The following are examples of radiology tests:

- X rays take pictures of the inside of the body to help diagnose problems. A chest X ray often is done to check for pneumonia or acute chest syndrome in children with sickle cell disease.
- CT scans are used less frequently but may be helpful at times. A CT scan takes multiple cross-sectional pictures that are put together by a computer to give a better idea of what soft tissues, bones, and organs look like. The results are sometimes more helpful than an X ray's results.
- MRI uses a magnetic field and radio waves to produce images similar to those of a CT scan. MRI is used when a CT scan or X ray is unable to give enough detailed information.
- Ultrasound is a test that uses sound waves to produce images of the inside of your child's body. An abdominal ultrasound may be performed to determine the presence of gallstones.
- TCD is an ultrasound technique that looks at the blood vessels of the brain and how well the blood flows to the brain. TCD is a very powerful screening tool used to detect the risk of stroke in a child with sickle cell disease (HbSS and HbS-β 0 thal).

Other Tests

- Echocardiography (ECHO) is a noninvasive way to look at the structure of the heart and how the blood flows through it. It is helpful for the early detection of pulmonary hypertension.
- Lung function tests (also called pulmonary function tests, or PFTs) show how well your child's lungs function.
- Polysomnography (also called a sleep study) diagnoses sleep disorders. This test can determine if your child is having trouble getting enough oxygen when asleep.
- Neuropsychological testing measures your child's strengths and weaknesses in areas such as learning abilities, language, memory, and attention span.

HOW IS SICKLE CELL DISEASE TREATED?

Penicillin

A major research study conducted in the 1980s found that penicillin taken twice a day until the age of 5 decreases the risk of death from infection by 84% in infants and toddlers living with sickle cell disease. Because of this study, many states began screening newborns for sickle cell disease so penicillin could be started right away. These newborn-screening programs have improved the survival rate in early childhood. Penicillin (taken twice a day), caregiver education, and immunization with the pneumococcal vaccine polyvalent (Pneumovax 23) have made a huge improvement in the health of babies born with sickle cell disease.

Folic Acid

Folic acid is a vitamin needed to make hemoglobin. Because children with sickle cell disease need to make more hemoglobin, they need more folic acid. Often, the hematologist will prescribe a folic acid pill to take once a day.

Pain Medication

Pain crisis or vaso-occlusive crisis is the number one reason children with sickle cell disease seek medical attention or come to the hospital. However, some pain can be managed at home with medications prescribed by your child's hematology team. It is important to know that pain can be reduced and managed but not always eliminated. The goal of pain management is to decrease pain to allow for improved patient function and mobility and to allow the ability to cough and take deep breaths to avoid complications like acute chest syndrome.

There are two main types of pain medications prescribed. The first is nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin®, Advil®), ketorolac (Toradol®), and naproxen sodium (Aleve®, Naprosyn®). These medications are helpful in reducing some of the swelling and inflammation associated with pain crisis as well as relieving the pain. The second group of medications is opioid pain relievers such as morphine, hydromorphone (Dilaudid®), and oxycodone (included in Percocet®, OxyContin®). Acetaminophen (Tylenol®) with codeine rarely is used because of how it is absorbed by the body, not relieving pain for some patients and lasting longer than is safe for others.

In cases when pain crises are not well controlled, adding opioids like morphine, oxycodone, and hydromorphone to a Tylenol or Motrin regimen may be more effective in relieving the pain. Although adding these medications has the potential for patients to become tolerant and dependent, but rarely addicted, they are safe when used as prescribed. *Tolerance* means the body gets use to a medication and more is needed to treat the pain or a different medication is needed. *Dependence* refers to a state of needing a medication to function normally and the patient having distressing physical symptoms when the medication is taken away. Your child's hematology team can address these issues in more detail.

Other prescription drugs that may be used when adequate pain control is not possible are ketamine and gabapentin. Ketamine is a medication used for anesthesia; however, low doses of ketamine in conjunction with opioids can be used to treat acute pain in patients with sickle cell disease in acute settings, such as the emergency room and hospital. Gabapentin is an anti-seizure medication used to treat neuropathic or nerve pain. It also can be used to help treat chronic pain (pain lasting longer than 3 months) in patients with sickle cell disease.

In the hospital, a patient-controlled analgesic (PCA) pump often is used to deliver pain medications (usually morphine or hydromorphine [Dilaudid]) as either "frequent" small infusions (on demand) controlled by the patient or as a small continuous infusion. The nurse programs and changes the settings of the PCA pump based on your child's pain level and use of the pump.

Pain medications may have side effects. The most common side effects are itching, upset stomach, constipation, and sleepiness. If your child is experiencing any of these side effects, speak with your child's hematology team, and they will help your child with these side effects or even prescribe a different medication.

There are also alternative treatments for sickle cell pain other than medications. Studies have shown that complementary alternative medicine (CAM) approaches have been useful alone and with medications for pain. These include heat application, distraction, acupuncture, aromatherapy, and healing touch. Other useful approaches are prayer, spiritual and energy healing, relaxation techniques, exercise, diet, and herbal medicines. Always consult your child's hematology team to learn which approaches may be helpful for your child.

Transfusion

Occasionally, a transfusion of red blood cells may be needed to treat certain situations and complications of sickle cell disease. This transfusion will be given into a vein over the course of 2–4 hours. Transfusions may be planned in advance, as is the case before some surgeries; however, a transfusion also may be needed in an emergency situation. Individuals who have had strokes or an abnormal TCD likely will require chronic (every 2-4 weeks) transfusions for a period of time. If you have any questions or concerns about transfusions, talk to your child's hematology team before an emergency happens.

Hydroxyurea

Before a child is born, their red blood cells contain fetal hemoglobin (hemoglobin F). If a child is born with sickle cell disease, this hemoglobin F is replaced by hemoglobin S in the first few months of life. Some people inherit the ability to keep making a small amount of hemoglobin F. As they get older, these people tend to have fewer complications of sickle cell disease. A medication, hydroxyurea, was found to stimulate the production of hemoglobin F. Hydroxyurea is a medication that has been found to turn on the body's production of hemoglobin F. When taken correctly and monitored carefully, hydroxyurea does not have serious side effects. Hydroxyurea has been shown in research studies to decrease the number of pain episodes, the need for transfusions and hospitalizations, and incidences of acute chest syndrome. Hydroxyurea is approved by the U.S. Food and Drug Administration (FDA) and has been found to be safe to use even in very young children. Because it can harm a fetus, hydroxyurea should not be taken by people who are pregnant or plan to become pregnant.

Endari

Endari®, an amino acid (also called L-glutamine), is a drug approved by the FDA in 2017 to treat sickle cell disease. Endari is a powder taken by mouth twice a day that helps to decrease the number of pain episodes in patients with sickle cell disease who are 5 years of age and older. It is important to take all medications as prescribed. Talk to your child's hematology team to find out if this medication is right for your child.

ADAKVEO (Crizanlizumab-tmca)

ADAKVEO® is an infusion drug approved by the FDA in 2019 to help reduce how often pain episodes occur in patients with sickle cell disease. ADEKVEO works by making blood vessels and certain blood cells less sticky. It is approved as a once-monthly infusion to be used in patients 16 years of age and older. The infusion must be given by a healthcare provider. Talk to your hematology healthcare team to find out if ADEKVEO can be given to your child.

Oxbryta (Voxelotor, GBT440)

Oxbryta® is an oral drug (to be taken by mouth) approved by the FDA in 2019 to treat sickle cell disease in patients 12 years of age and older. It helps hemoglobin hold on to oxygen and helps prevent the red blood cells from becoming sickled. Oxbryta also should help reduce the risk of pain crises caused by sickle cells blocking small blood vessels. Your hematology healthcare provider can give you more information on this drug.

Stem Cell Transplant

Stem cell transplant is the only cure for sickle cell disease. Because stem cell transplant has the potential for very serious side effects, it most often is used for those with severe sickle cell disease. However, there is research looking closely into the benefits of stem cell transplant before significant complications from the disease are experienced. Before a stem cell transplant, the child will be given chemotherapy and/or radiation to destroy their own bone marrow (where blood cells are made). He or she then receives an infusion of a donor's stem cells. In the weeks to months following the transplant, the donor cells take over and produce blood cells that are unaffected by sickle cell disease.

Stem cell transplant does have risks, including serious infection, bleeding, and organ damage from the chemotherapy and radiation. Graft-versus-host disease, a condition in which the donor's stem cells begin to attack the patient's body cells, also may develop. In some cases, these complications can be fatal. Additionally, the stem cells may not "take," which is a condition called graft failure.

WHAT RESEARCH IS TAKING PLACE?

Fortunately, there is a great deal of research being done in the area of sickle cell disease. For instance, studies are taking place to improve and limit the side effects of current treatments and additional research is looking at new treatment options.

Endothelial Dysfunction and Nitric Oxide

Research is showing that sickle cell disease is not simply a disease of red blood cells but also a disease of the blood vessels and their lining, or *endothelium*. When sickled red blood cells come into contact with the endothelium, they cause inflammation. If the endothelium becomes inflamed, the space in which the blood has to travel becomes narrower and makes a blockage of sickled cells more likely.

Nitric oxide is an important substance in the body. It helps keep blood vessels open, allowing blood to flow freely. Nitric oxide also decreases certain proteins that cause red blood cells to stick to the endothelium. Scientists have found that people with sickle cell disease have less nitric oxide than those without the condition.

Researchers are looking at ways to decrease the inflammation of the endothelium and to increase the levels of nitric oxide in people with sickle cell disease.

Gene Therapy

In 1997, researchers figured out how to insert the gene for sickle cell disease into mice. Then in 2001, scientists had another breakthrough and were able to correct the sickle cell gene in the affected mice. Today, research continues to move toward the next extremely difficult step, which is to take that corrected gene and insert it into the DNA of a human with sickle cell disease.

Patients with sickle cell disease have better access to gene therapy studies due to the positive research in this area and a better understanding of gene therapy itself. Clinical trials are now available at a few hospital centers for children and adults with sickle cell disease. However, the high cost of gene therapy may limit its availability of in the future. Ongoing studies are in place to address these issues.

Genetic Factors

Although every person with sickle cell disease inherits the same gene mutation, they do not all have the same symptoms and complications. People from the same part of the world and same racial background seem to have similar health problems, which is probably because of other genetic traits that impact sickle cell disease. As scientists learn more about the genetic traits associated with different complications, they will know more about predicting how an individual's sickle cell disease might "behave." In the future, treatment may be customized based on the genes a person has inherited along with the genes for sickle cell disease. Then, treatments such as stem cell transplant, gene therapy, and hydroxyurea therapy may be initiated before complications occur, not in response to complications occurring.

Treatments such as stem cell transplant, gene therapy, and hydroxyurea therapy may then be initiated before complications occur and not because of them.

HOW CAN I HELP MY CHILD STAY WELL?

Newborn screening has resulted in children being referred shortly after birth to centers where care is delivered using a team approach. Experienced hematologists, nurse practitioners (or physician assistants), nurses, nutritionists, social workers, and other members of the healthcare team address all aspects of care. Access is provided to the screening tests and other specialists who will be involved in your child's care. These centers most often are located within the hospital where your child will be admitted, ensuring seamless care.

It is important for your child to see their hematology team on a regular basis, even if he or she is doing well. The team will provide the education you need to care for your child in the best way. Also, the ongoing screening and testing done at these well visits is needed for the prevention and early detection of long-term complications.

Your child will continue to be monitored by their primary care doctor for all routine care that is unrelated to sickle cell disease. This includes immunizations, checkups, and treatment for minor illnesses or injuries. It is very important to keep up to date with immunizations because these will help your child avoid serious infections. In addition to the immunizations all children receive, your child also should receive the pneumococcal vaccine polyvalent (Pneumovax® 23) at ages 2 and 5. Your child also will receive the meningococcal vaccine. This will provide extra protection against the bacteria that threaten children with sickle cell disease who do not have well-functioning spleens. Your child also should have an annual flu shot.

Avoiding situations that can lead to medical emergencies is very important. This means making sure your child rests as needed, stays well hydrated, and dresses properly for the weather. Teach your child good hand-washing and hygiene techniques to avoid the spread of infection.

Simple Dos and Don'ts

- Always keep your child dressed warmly during cold weather.
- Keep your child out of extreme heat to avoid dehydration.
- Ensure your child drinks plenty of fluids. Always encourage kids to have a water bottle with them.
- Do not let your child sit around in a wet bathing suit. Dry them off immediately after getting out of the pool or at the beach.
- Make sure your child gets adequate sleep.
- Keep medications (Advil, Motrin, or other pain medications) readily available.

IS MY CHILD'S DIET IMPORTANT?

Your child should eat a well-balanced diet that has the number of healthy calories advised for their age. He or she also should take a daily folic acid supplement, if prescribed. During each visit to your hematology team, your child will be weighed and measured. Your child will need the support of a nutritionist if he or she is not growing or gaining weight. It is important to maintain a healthy weight because obesity can lead to stress on the joints and heart as well as conditions such as hypertension and diabetes.

Drinking fluids, especially water, is very important for your child because dehydration can lead to sickling of red blood cells. This is especially true during stressful times, such as pain crisis, illness, or being in hot weather. Caffeinated and sugary beverages should be avoided. Eating a well-balanced diet, including fruits and vegetables, and drinking plenty of water are important to avoid constipation, which can cause abdominal pain. Talk to your hematology team or primary provider if your child has constipation or abdominal pain.

ARE MY FEELINGS NORMAL?

Feelings of guilt, fear, worry, and helplessness, among others, are common when you have a child living with sickle cell disease. Even though sickle cell disease is a serious condition, you should know there are many steps you can take to help improve your child's quality of life.

It helps to develop strong relationships with healthcare providers who can answer questions and provide treatment for your child. Your hematology team may be able to introduce you to other parents and children affected by sickle cell disease so you can share information, offer support, and give practical advice to one another.

Sometimes parents are anxious about what might happen to their child because they do not have sufficient or accurate information about sickle cell disease. Many parents find it helpful to learn as much as they can about sickle cell disease. Learning how to help prevent pain and to palpate (feel) the spleen are important to keep your child healthy. You should take your child for regularly scheduled checkups with a hematology provider. You can work with your child's hematologist and sickle cell disease team to learn more about what you can do to help your child stay healthy. This way, you also will be able to help your child receive care quickly if problems develop.

Having a child with a chronic illness can trigger many emotions. Because sickle cell disease is inherited, some parents feel guilty about having "given" the disease to their child. Some parents find support in their church or other faith community as well as from their child's school counselor, social worker, and nurse. You might want to attend support groups with other parents of children with sickle cell disease. Don't be shy about asking questions or seeking help for yourself and your child.

You are an important role model for your child. When your child sees how you get information and guidance for making decisions about keeping him or her healthy, your child learns good self-care habits. Seeing you take good care of your own health and enjoy your life helps to motivate your child to follow in your footsteps.

The unknown can be frightening to children. Be honest when your child asks questions about sickle cell disease, its treatment, and its complications. Educate your child about sickle cell disease in age-appropriate words. This will help him or her feel empowered and in control. Keeping your child's developmental level in mind, allow him or her to assume responsibility for some aspects of care. This will help prepare your child for the transition of having to care for himself or herself as adulthood approaches.

CAN MY CHILD ATTEND SCHOOL?

School is an important part of every child's life. In addition to learning about reading, writing, and math in school, children also learn how to get along with others. Living life in ways that are similar to their siblings and peers also gives children an important feeling of being included in the "regular" world and helps them feel safe. Children who feel included and safe grow up feeling comfortable asking for help and wanting to contribute to their community.

You can help your child participate in activities that build self-esteem and self-reliance. Your child's hematology team may recommend limiting some kinds of activities; however, you can explore alternatives that will give your child opportunities to develop skills and talents outside of the classroom.

At the start of the school year, consider meeting with your child's teacher, principal, and school nurse. Beginning with preschool and kindergarten, you can help educate school personnel about sickle cell disease by giving them educational materials provided by your sickle cell disease team. Sometimes nurses and social workers from your team can call or visit your child's school and talk to your child's teachers about sickle cell disease. Ask them to share the information with others in the school. They can learn about the disease and provide support to your child during the school day.

Although children with sickle cell disease may miss some school because of doctors' visits and times when they do not feel well, it is beneficial for them to attend school as much as possible. After an illness or painful episode, it is best to send your child back to school as soon as possible. In general, children are better off when they attend school regularly.

If your child is not doing well in school, talk with their teachers. Your child may need to be tested for learning difficulties. Children with learning difficulties often need individualized educational plans (IEPs) to help them succeed in school.

You can talk to members of your child's healthcare team about information they might want to share with the school to make sure your child's educational and health needs are addressed. For instance, children with sickle cell disease should be allowed to have water at their desk and to go to the bathroom more frequently than their classmates. They should never have ice applied to an injury. They also should be encouraged to participate in all class activities unless advised otherwise by their sickle cell team. Each child is unique, and there may be other ways an educational plan can be designed to help your child. Your child may need tutoring to help catch up after missing school because of illness. Ask the school and your healthcare team if there are tutoring programs at school or in the hospital. Aim for your child to be healthy, happy, and successful and work with your child's healthcare team to provide the kinds of support your child deserves.

TRANSITIONING FROM PEDIATRIC TO ADULT CARE

When your child becomes an adult (usually at age 18), they may have to move from pediatric to adult hematology care. This can be a challenging and difficult process. You and your adolescent or young adult may experience fear and anxiety during this time. However, this should be viewed as a natural process, like a graduation. Poor transition to adult care has been linked to a decrease in health quality, increased emergency room visits, and increased hospitalizations and healthcare costs. Successful transition has been linked to better health outcomes and better quality of life. Check to see if your child's hospital has a transition program. Transitioning should include developing skills and knowledge to not only move to an adult hematology provider but to learn how to self-manage sickle cell disease. Work with your hematology team to help your adolescent or young adult develop self-management skills and be adequately prepared to transition to adult hematology care when it's time.

ONLINE RESOURCES

Centers for Disease Control and Prevention; Tips for Supporting Students with Sickle Cell Disease
https://www.cdc.gov/ncbddd/sicklecell/documents/tipsheet_supporting_students_with_scd.pdf

KidsHealth for Parents—Sickle Cell Disease
http://kidshealth.org/parent/medical/heart/sickle_cell_anemia.html

National Heart, Lung, and Blood Institute; National Institutes of Health—Sickle Cell Disease
www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA_WhatIs.html

Center of Parent Information & Resources; Parent Training and Information Center
www.parentcenterhub.org/find-your-center

Sickle Cell Disease Association of America, Inc.
www.sicklecelldisease.org

The Sickle Cell Information Center
www.scinfo.org

Be the Match; Sickle Cell Disease (SCD)
https://bethematch.org/patients-and-families/about-transplant/blood-cancers-and-diseases-treated-by-transplant/sickle-cell-disease--scd-/

Website URLs correct and active as of July 2020.

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