

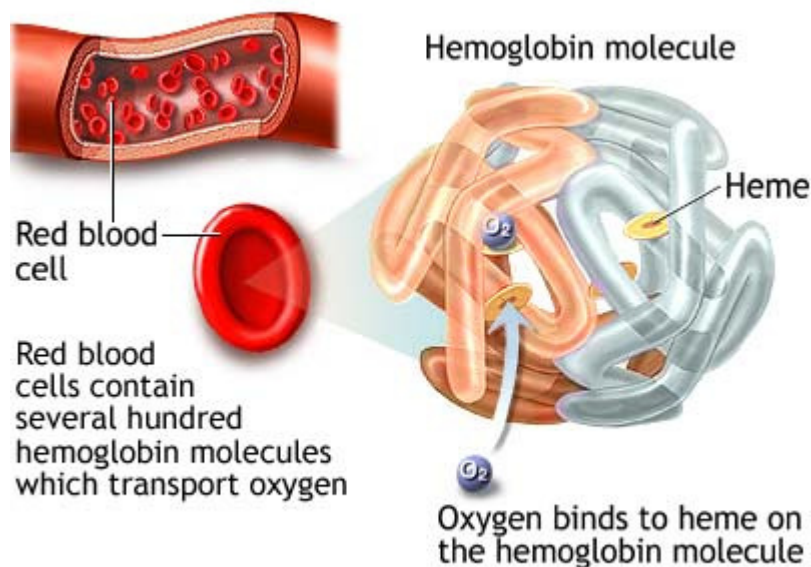
Sickle Cell Disease In-Depth

(www.whatsyourph.com)



Hemoglobin is a complex molecule and the most important component of red blood cells. Sickle cell disease occurs from genetic abnormalities in hemoglobin. Three forms of hemoglobin are important in this disorder:

- *Hemoglobin A (HbA)*. HbA is the hemoglobin molecule found in normal red blood cells during childhood and adulthood.
- *Hemoglobin S (HbS)*. HbS (S is for sickle) is the abnormal variant of hemoglobin A, which occurs in sickle-red blood cells and is the primary characteristic of the disease. The difference between hemoglobin A (HbA) and hemoglobin S (HbS) lies in only one protein out of about three hundred that are common to both. This protein lies along an amino-acid chain called beta-globin, where even a tiny abnormality has disastrous results.
- *Hemoglobin F (HbF)*. HbF (F is for fetal) is a form of hemoglobin that is produced in everyone during fetal development in the womb and for a short time after birth. Normally, most HbF is later replaced by hemoglobin A, although some HbF may persist throughout life. Importantly, HbF is able to block the sickling action of red blood cells. Infants who have inherited sickle cell disease, then, do not develop symptoms of the illness while they still have HbF. People with the sickle cell gene who continue to carry some fetal hemoglobin are better protected, therefore, from severe forms of the disease. It is being used as the basis for therapies used in sickle cell.



Hemoglobin is the most important component of red blood cells. It is composed of a protein called heme, which binds oxygen. In the lungs, oxygen is exchanged for carbon dioxide. Abnormalities of an individual's hemoglobin value can indicate defects in red blood cell balance. Both low and high values can indicate disease states.

Changes that Lead to Sickle Cell Disease

Sickle cells disease is a result of changes in hemoglobin S:

- The destructive nature of the sickle hemoglobin develops when it loses oxygen.
- The deoxygenated molecules form rigid rods called *polymers* that distort the red blood cells into a sickle or crescent shape. This process is called *polymerization* and is the primary change leading to disease and destruction.
- These abnormally sickle-shaped cells are both rigid and sticky. They stick to the walls and cannot squeeze through the capillaries. Blood flow becomes obstructed, depriving tissues and organs of oxygen. In the immediate setting, oxygen deprivation (hypoxia) can cause severe pain (the sickle cell crisis). Over time, it leads to chronic and progressive destruction in organs and tissues throughout the body.



Click the icon to see an image of sickle cells.

- In a vicious cycle, oxygen deprivation in cells leads to more polymerization and increased production of sickle cells. The higher the concentration of sickle hemoglobin and the more acidic the environment, the faster the sickle cell process. (Fortunately, in most cases the majority of blood cells have traveled out of the capillaries before they have time to be affected, and only about 20% of all red blood cells polymerize and become sickle-shaped.)
- Excessive acidity and the abnormal shape of the sickle cell also cause water and potassium loss from the cell, resulting in dehydration. Cell dehydration is another major destructive factor in the sickling process of red blood cells. To maintain the proper inflow and outflow of water, a cell uses a pump controlled by calcium and potassium. Potassium can be lost and calcium increased through a number of mechanisms. These minerals have electric charges that open and close a channel known as the Gardos channel in the cell membrane. If there is too little potassium and too much calcium in the bloodstream, the channel doesn't close and water flows out. The resulting dehydration increases the density of hemoglobin S within the cell, thereby speeding up the sickling process.
- High levels of hemoglobin S are released from red blood cells into the bloodstream. Importantly, hemoglobin eliminates nitric oxide, a soluble gas that prevents blood clotting and keeps the blood vessels flexible. Deficiencies in nitric oxide, which can result in severe narrowing of blood, are an important cause of the intense pain in sickle cells disease. In adults, men may be more susceptible to this effect than women.
- Sickle cells also have a shorter life span (10 to 20 days) than that of normal red blood cells (90 to 120 days). Every day the body produces new red blood cells to replace old ones, but sickle cells become destroyed so fast that the body cannot keep up. The red blood cell count drops, which results in anemia. This gives sickle cell disease its more common name, *sickle cell anemia*.

- The sickle cell disease process is triggered when red blood cells become deprived of oxygen. When they are re-exposed to oxygen, the polymerized hemoglobin molecules fall apart into harmless forms.

The severity of sickle cell disease generally depends on a number of factors:

- *The extent of oxygen loss.* Prolonged oxygen deprivation contributes to the severe pain experienced as a sickle cell crisis. It also produces both short- and long-term organ damage. The lungs are specifically critical targets of the disease process. Because they supply oxygen, they can restore the sickle molecules to a normal form. Unfortunately, once the process occurs, the lungs become major sites for sickle cell damage, particularly for dangerous acute episodes of chest pain.
- *The acidity of the environment.* The lower the better. The organs most seriously affected are those with an acidic environment (such as the spleen and bone marrow).
- *The concentration of hemoglobin S within the cell.* The lower the better.
- *The amount of a protective hemoglobin F (for fetal).* The more the better.

Blood

Blood has two major components:

- Plasma is a clear yellow liquid that contains proteins, nutrients, hormones, electrolytes, and other substances. It constitutes about 55% of blood.
- White and red blood cells and platelets make up the balance of blood. The white cells are the infection fighters for the body, and platelets are necessary for blood clotting. The important factors in anemia, however, are red blood cells.

Red blood cells (RBCs), also known as *erythrocytes*, carry oxygen throughout the body to nourish tissues and sustain life. Red blood cells are the most abundant cells in our bodies; men have about 5,200,000 and women have about 4,700,000 per cubic millimeter of blood. To understand red blood cells and their role in anemia, it is useful to know certain facts about them.

Hemoglobin and Iron

Each red blood cell contains between 200 and 300 *hemoglobin* molecules. Hemoglobin is a complex molecule and the most important component of red blood cells. It is composed of protein (*globulin*) and a molecule (*heme*), which binds to iron.

In the lungs, the heme component binds to oxygen in exchange for carbon dioxide. The oxygenated red blood cells are then transported to the body's tissues, where the hemoglobin releases the oxygen in exchange for carbon dioxide, and the cycle repeats. The oxygen is used in the *mitochondria*, the power source within all cells.

Red blood cells typically circulate for about 120 days before they are broken down in the spleen. Most of the iron present in hemoglobin can be recycled and reused.

Structure and Shape

Red blood cells are extremely small and look something like tiny, flexible inner tubes. This unique shape offers many advantages:

- It provides a large surface area to absorb oxygen and carbon dioxide.
- Its flexibility allows it to squeeze through capillaries, the tiny blood vessels that join the arteries and veins.

- Abnormally shaped or sized erythrocytes are typically destroyed and eliminated.

Blood Cell Production (Erythropoiesis)

The actual process of making red blood cells is called *erythropoiesis*. (In Greek, *erythro* means "red" and *poiesis* means "the making of things.") The process of manufacturing, recycling, and regulating the number of red blood cells is complex and involves many parts of the body:

- The body carefully regulates its production of red blood cells so that enough are manufactured to carry oxygen but not so many that the blood becomes thick or sticky (*viscous*).
- Most of the work of erythropoiesis occurs in the bone marrow. In children younger than 5 years old, the marrow in *all* the bones of the body is enlisted for producing red blood cells. As a person ages, red blood cells are eventually produced only in the marrow of the spine, ribs, and pelvis.
- If the body requires an increase in oxygen (at high altitudes, for instance), the kidney triggers the release of *erythropoietin* (EPO), a hormone that acts in the bone marrow to increase the production of red blood cells.
- The life span of a red blood cell is between 90 and 120 days. Old red blood cells are removed from the blood by the liver and spleen.
- There they are broken down and iron is returned to the bone marrow to make new cells.

Oxygen Loss in Red Blood Cells with Normal Hemoglobin

In everyone, hemoglobin loses its oxygen normally in a number of ways:

- To sustain life, oxygen regularly passes from red blood cells to the tissues where it is needed to perform vital functions.
- Hemoglobin loses oxygen if blood cells become too acidic, for example, after strenuous exercise.
- Going to high altitudes or any stressful activity or situation that increases the body's demand for oxygen depletes its supply in red blood cells.

Such situations do not affect normal red blood cells that contain hemoglobin A.

Risk Factors

Sickle cell disease is inherited. People at risk for inheriting the gene for sickle cell descend from people who are or were natives of Africa and parts of India and the Mediterranean. The sickle cell gene also occurs in people from South and Central America, the Caribbean, and the Middle East. The high incidence of the sickle cell gene in these regions of the world is due to the sickle cell's ability to make red blood cells resistant to the malaria parasite:

- People who inherit just a single gene are referred to as having the *sickle trait*. These people are protected against malaria and do not develop sickle cell disease. About 40% of people in certain parts of Africa and about 9% of African Americans have the trait.
- Those who inherit both copies of the HbS gene develop sickle cell disease. They are not protected from malaria, however. In fact, malaria is more serious in these individuals. An estimated one in every 500 African Americans and one in every 1,000 to 1,400 Hispanic Americans are born with sickle cell disease itself.

Risk in Children of Parents with the Sickle Cell Gene

The sickle cell gene for hemoglobin S (HbS) is the most common inherited blood condition in America. About 72,000 Americans -- mostly African Americans -- have sickle cell disease. The risk for inheriting sickle cell disease from parents with the sickle cell gene is as follows:

- One parent has only one copy of the sickle cell gene and the other parent has two normal hemoglobin genes, and the child inherits a healthy gene from each parent. The child will not inherit either the disease or the trait.
- The child inherits one copy of the sickle cell gene. The child has the trait (HbS) only. The other, healthy hemoglobin gene overrides HbS and blocks the development of sickle cell disease. Such people lead normal lives.
- The child inherits the hemoglobin S gene from both parents (HbSS). The child develops the full-blown disease. (If each parent has one copy of the gene, the child has a 25% chance of acquiring the disease.)
- The child inherits one hemoglobin S gene and one abnormal hemoglobin gene from other causes (such as one form called HbSC). Such children may develop a form of sickle cell disease. It is often a milder variant but children can experience severe symptoms. They are also at risk for some of the complications of sickle cell disease, although their risks for serious problems are lower than in children with the full-blown disease.

Symptoms

General Symptoms in Infants. In infants, symptoms do not usually appear until late in the baby's first year. Most commonly, they are the following:

- Fever
- Swelling of the hands and feet
- Pain in the chest, abdomen, limbs, and joints
- Nosebleeds and frequent upper respiratory infections

General Symptoms in Childhood. Pain is the most common complaint. It can be acute and severe or chronic, usually from orthopedic problems in the legs and low back. Other symptoms include:

- Anemia
- Fatigue
- Irritability
- Jaundice (yellowish discoloration of the skin and eyes)
- Bedwetting

Additional Symptoms in Adolescence or Adulthood. Symptoms of childhood continue in adolescence and adulthood. In addition, patients may experience:

- Delayed puberty (in young teenagers)
- Severe joint pain
- Progressive anemia
- Leg sores
- Gum disease

Sickle Cell Crisis

The hallmark of sickle cell anemia is a group of devastating symptoms known collectively as a *sickle cell crisis* (also sometimes known as a *vaso-occlusive crisis*). Sickle cell crises are episodes of pain that occur

with varying frequency and severity in different patients and are usually followed by periods of remission. Severe sickle cell pain has been described as equivalent to cancer pain and more severe than postsurgical pain. It most commonly occurs in the lower back, leg, abdomen, and chest, usually in two or more locations. Episodes usually recur in the same areas.

The risk for a sickle cell crisis is increased by any activity that boosts the body's requirement for oxygen, such as illness, physical stress, or being at high altitudes. In more than half the cases, however, the trigger is unknown. Acute chest syndrome is a particularly serious complication of sickle cell crisis. It occurs in the lungs and can be extremely serious and even life threatening.

Diagnosis

Prenatal diagnosis of sickle cell disease is now possible for women who may be at risk for having a child with the disease. A positive result for sickle cell disease, however, poses extremely difficult questions even for parents who are not opposed to abortion:

- Some cases of sickle cell disease can be mild, but the parents and doctors have no way of knowing this from test results.
- The benefits of current treatments and pain management must be weighed against the likelihood of suffering and a shorter life span for their child.
- Parents who choose to keep the child must be prepared to be vigilant and aggressive partners with their doctors. In spite of their own emotional anguish, they must be loving and fully supportive when their child is suffering a sickle cell crisis.
- Energy, time, and money are necessary expenditures in raising any child; they are significantly increased when a child has this severe and life-threatening illness.

A genetic test known as preimplantation genetic diagnosis (PGD) may prove to determine the presence or absence of the sickle cell mutation in embryos (fertilized eggs) before they are implanted in the mother during assisted fertilization techniques. This genetic tool may eventually help avoid the often emotionally devastating effects of abortion.

Screening Tests for Newborns

Most states, though not all, now screen infants for sickle cell disease. The earlier a child is diagnosed with sickle cell disease, the higher the survival rate. States where screening is now required report survival rates in children with sickle cell disease that are equal to those of African-Americans without the disease. To perform the test, a blood sample is taken from the baby's heel using a simple needle prick.

Ruling Out Other Diseases

As part of the diagnosis, the doctor will rule out other conditions that resemble sickle cell disease. It is sometimes difficult to distinguish between abnormalities in the bone caused by infection and those caused by a sickle cell crisis. Bone scans may be performed to help diagnose possible bone infections. Other disorders that might mimic certain stages of sickle cell disease include some types of anemia, rheumatic fever, hepatitis and other liver diseases, and infections of the kidney or heart. Other genetic abnormalities can cause sickling of the red blood cells, including hemoglobin C, hemoglobin I, and high levels of Bart's hemoglobin.

Outlook

New and aggressive treatments for sickle cell disease are prolonging life and improving its quality. As recently as 1973, the average lifespan for people with sickle cell disease was only 14 years. Currently, life expectancy for these patients can reach 50 years and over. Early studies showed that women had a

greater risk for death from sickle cell disease than men, but experts now believe this was due to high mortality during pregnancies before the mid 1970s. Women with sickle cell disease now actually live longer than their male counterparts.

Acute Attacks

The damage and durability of sickle cell disease occurs because the logjam that sickle cells cause in the capillaries slows the flow of blood and reduces the supply of oxygen to various tissues. Not only does pain occur when body tissues are damaged by lack of oxygen, but serious and even life-threatening complications can result from severe or prolonged oxygen deprivation. Sickle cell disease is referred to in some African languages as "a state of suffering," but the disease has a wide spectrum of effects, which vary from patient to patient. In some people, the disease may trigger frequent and very painful sickle cell crises that require hospitalization. In others, it may cause less frequent and milder attacks.

Effects of the Disease Process Over Time

Children with sickle cell disease are very susceptible to infections, usually because their damaged spleens are unable to protect the body from bacteria. A recent study suggested that signs of impaired lung function occurred even in very early years. As medical progress has increased the lifespan of children with sickle cell disease, older patients are now facing medical problems related to the long-term adverse effects of the disease process. The most serious dangers are from acute chest syndrome, long-term damage to major organs, stroke, and complications during pregnancy such as high blood pressure in the mother and low birth weight.

Advances in screening for organ complications, in new medications, and in transfusion and transplantation techniques are showing great promise for improving survival rates and quality of life.

Complications

There is still no cure for sickle cell disease other than experimental transplantation procedures, but treatments for complications of sickle cell have prolonged the lives of many patients who are now living into adulthood.

Pain and Acute Sickle Cell Crisis

The hallmark of sickle cell disease is the *sickle cell crisis* (also sometimes known as a *vaso-occlusive crisis*), which is an episode of pain. It is the most common reason for hospitalization in sickle cell disease. The pattern may occur as follows:

- In general, the risk for a sickle cell crisis is increased by any activity that boosts the body's requirement for oxygen, such as illness, physical stress, or being at high altitudes. In more than half of episodes, however, the trigger is unknown.
- Episodes typically begin at night and last from three to 14 days, accelerating to a peak over several days and then declining.
- The pain is typically described as sharp, intense, and throbbing. Severe sickle cell pain has been described as equivalent to cancer pain and more severe than postsurgical pain. Shortness of breath is common.
- Pain most commonly occurs in the lower back, leg, hip, abdomen, or chest, usually in two or more locations. Episodes usually recur in the same areas. Pain in the bones (usually occurring symmetrically on both sides) is common because blood obstruction can directly damage bone and because bone marrow is where red blood cells are manufactured.

- The liver may become enlarged, causing pain in the upper right side of the abdomen. Liver involvement may also cause nausea, low-grade fever, and increasing jaundice.
- Males of any age may experience prolonged, often painful erections, a condition called priapism.

Episodes cannot be predicted and they vary widely among different individuals. In one study, nearly 40% of patients reported no painful episodes over a five-year period. About 5% of patients experienced severe and frequent episodes (more than three a year). They sometimes become less frequent with increasing age. Generally, people can resume a relatively normal life between crises. Most patients are pain free between episodes although pain can be chronic in some cases.

General Guidelines for Managing a Sickle Cell Crisis. The basic objectives for managing a sickle cell crisis are control of pain and rehydration by administration of fluids. Oxygen is typically given for acute chest syndrome. Effective pain medications are available to help reduce the severe pain of sickle cell crises.

Accurate and continually updated assessment of pain determined by patient input and participation is at the crux of effective care for children with sickle cell disease. Often, however, patients are not given the treatment they require. According to one study, for example, 71% of children were inadequately treated for their pain. Possible reasons for this are as follows:

- Many patients, their families, and even doctors are hesitant to use opioids aggressively because of fear of addiction. This fear, however, is nearly always unwarranted. Addiction occurs in only about 1 - 3% of patients with sickle cell disease who are taking opioids.
- Many doctors do not understand the nature of sickle cell pain. For example, early phases of sickle cell crisis can cause severe pain before test results confirm a diagnosis of a crisis. In such cases, health professionals may question the patient's self-reporting and withhold appropriate pain medication.
- Patients may behave normally (e.g., talking on the phone, sleeping) and not appear to be in pain, but have actually developed coping behaviors to allow them to function in spite of severe pain.
- Children and adults report pain differently, with children tending to report less pain than they feel. (One way of determining the severity of pain that a child feels is to show pictures of faces demonstrating degrees of pain and asking the child to point to the one that best expresses his or her experience.)
- Many patients use emergency rooms of large hospitals for treating acute pain. Waiting times are long and there is no single health care provider who knows the patient and can offer consistent assessment and management of pain.

Adult patients and parents of children with the disease should insist on aggressive pain-relief treatment. If doctors show any reluctance to administer medications after the onset of pain, patients or caregivers should not hesitate to seek a more responsive health care professional.

Opioids. For severe pain, the patient must be hospitalized and treated with strong painkillers, usually opioids. Opioids are generally given orally to adults and adolescents and intravenously to children. Nevertheless, there are exceptions. Older patients with severe pain may also require intravenous administration. Studies are also suggesting that oral medications may be effective in children.

- Morphine (Dilaudid) is often used for frequent or prolonged episodes of pain. Unfortunately, its effectiveness is not as long-lasting in sickle cell patients as it is in other patients with severe pain, such as those with cancer.
- The opioid meperidine (Demerol) is also used for sickle cell crises. Meperidine is not as powerful as morphine, however, and, if used for prolonged periods, may cause twitches, tremors, and disturbed mental states including seizures.
- Some newer synthetic opioids (fentanyl or hydromorphone) that have a rapid onset and possibly fewer side effects than morphine. Fentanyl can be applied using a patch, which may help some patients who have difficulty receiving intravenous drugs. It takes 12 hours to be effective, however.
- Oral drugs, such as methadone, oral morphine, codeine, and oxycodone, are useful for home management of chronic pain and for transitional treatments between the hospital and home. Tramadol (Ultram) is a potent oral painkiller that has opioid-like properties but is not as addictive. (Dependence and abuse have been reported, however.) It may be very useful for sickle cell patients who need painkillers outside the hospital. It has minimal effects on respiratory function and has a low potential for addiction.

The most dangerous side effect of high doses of opioids, especially morphine, is depression of breathing function. This can occur some time after the drug has been administered, and so patients must be watched closely and monitored during treatment.

Other side effects of opioids are vomiting and nausea, itching, and problems urinating. If the patient vomits or becomes nauseated, the doctor may administer prochlorperazine (Compazine). Devices have been developed to allow patients to administer their own painkillers as needed.

Anti-Inflammatory Drugs. Because of the potentially serious side effects of opioids, doctors are constantly searching for safer and easier ways of reducing the severity of pain of sickle cell crises. Because experts believe that inflammation is a major contributor to the pain of sickle cell disease, drugs that reduce inflammation are being studied.

- Prescription-strength NSAIDs, including diflunisal (Dolobid) or ketorolac (Toradol), are under investigation. Ketorolac may be particularly helpful in relieving bone pain, and may be effective for individuals who cannot tolerate opioids. In one study, it was superior to meperidine and had fewer side effects. Studies have suggested, however, that when used as first-line therapy in an acute crisis, ketorolac is effective only in about half of episodes.
- Corticosteroids are powerful anti-inflammatory drugs that are commonly used to treat pain caused by inflamed muscles and joints. Such drugs include methylprednisolone (Medrol) and dexamethasone (Decadron, Hexadrol). Studies are reporting that using these drugs along with opioids may help some sickle cell patients. In one study, children who were given methylprednisolone and morphine had a shorter period of severe pain and required less morphine to control the pain than those given morphine alone. These children, however, had more recurrent attacks after medication was withdrawn than those treated with opioids alone. Because steroids can suppress the body's infection fighters, they should not be given to patients with bacterial infections or any serious medical complication.

Epidural Anesthesia. An epidural analgesia (injection of an anesthetic into the spinal fluid) may be very effective for pain that is unresponsive to the usual therapies.

Stimulants. Some doctors report that stimulants, such as methylphenidate (Ritalin) and dextroamphetamine, may enhance the pain-killing effects of opiates and counteract the sleepiness they cause. Clinical studies are needed to confirm possible benefits, however.

Surfactants. Poloxamer 188 (FloCor, RheothRx) is an investigative synthetic compound known as a surfactant. It coats damaged blood cells, allowing them to slip over one another, thereby improving blood flow and oxygen delivery. Late clinical studies have been promising. A 2001 study reported that it reduced the duration of the crisis from 141 to 133 hours (which is still a long time). It was even more effective in children (reducing it to 21 hours) and in patients taking hydroxyurea (16 hours).

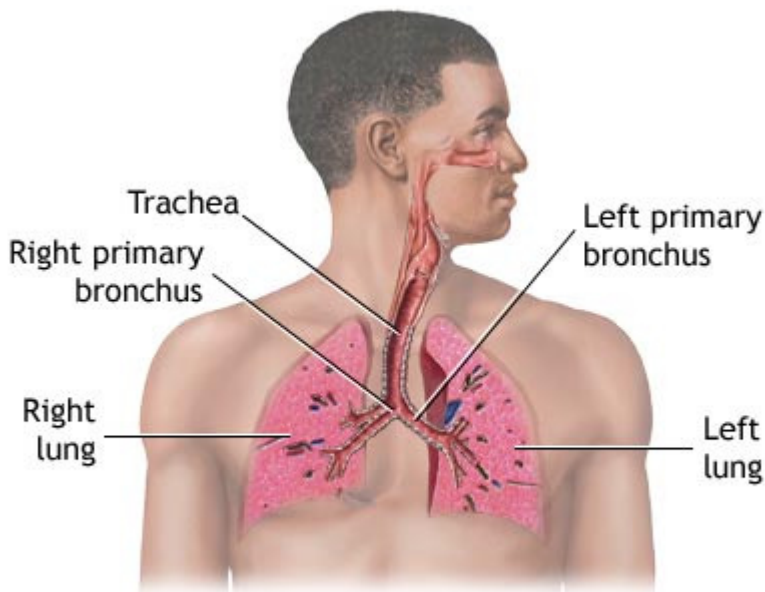
Cordox. A natural sugar-based compound called fructose-1,6-diphosphate, FDP (Cordox) reduces inflammation and protects cells against the oxygen-depriving effects of sickling. This drug also is investigative. Studies are indicating that it relieves vaso-occlusive pain. In one study, taking only one dose reduced pain scores. It is not addictive and does not appear to have significant adverse effects.

Acute Chest Syndrome

Acute chest syndrome (ACS) occurs when the lungs are deprived of oxygen during a crisis. It can be very painful, dangerous, and even life threatening. It is a leading cause of illness among sickle cell patients and is the most common condition at the time of death. At least one whole segment of a lung is involved and the following symptoms may be present:

- Fever of 101.3 F degrees (38.5 C) or above
- Rapid or labored breathing
- Wheezing or cough
- Acute chest pain

Pain often lasts for several days. In about half of patients, severe pain develops about two and a half days before there are any signs of lung or chest abnormalities. Acute chest syndrome is often accompanied by infections in the lungs, which can be caused by viruses, bacteria, or fungi. Pneumonia is often present. A dull, aching pain usually follows, which most often ends after several weeks, although it may persist between crises.



Air is breathed in (inhaled) through the nasal passageways, and travels through the trachea and bronchi to the lungs.

Causes of Acute Chest Syndrome. The two primary causes of acute chest syndrome are one or a combination of the following:

- Infection. Infection from viruses or small atypical organisms (*Chlamydia* and *Mycoplasma*) is the most common causes of the oxygen deprivation that leads to acute chest syndrome.
- Blockage of blood vessels. Blockage in the blood vessels (called *infarction*) that cuts off oxygen in the lungs is another important cause of acute chest syndrome. Blockage may be produced by blood clots or fat embolisms. (Fat embolisms are particles formed from fatty tissue in the bone marrow that enter and travel through the blood vessels.)

In about 45% cases, the cause cannot be established. Some cases of acute chest syndrome may result from treatments of the crisis, including from administration of opioids (which reduce oxygen) or excessive use of intravenous fluids. Other lung diseases may also trigger ACS.

Severity of Acute Chest Syndrome. The mortality rates for ACS are 1.8% in children and 4.3% in adults. The syndrome and its long-term complications are the major causes of death in older patients. In one major 2000 study, 13% of patients with acute chest syndrome needed mechanical ventilation for supporting their breathing, 11% had some neurologic symptoms, and it was fatal in 9% of adult patients. The condition is four times more deadly in adults than in children. The longer a patient survives, the greater is the damage done by repetitive sickle cell crises in the chest and lungs.

The following destructive effects can occur:

- Infarction or severe infection that cause the acute chest syndrome can be fatal.
- Lack of oxygen in the chest or in the bones cause severe pain.
- Damage in the chest area increases susceptibility to invading infections, even those that are ordinarily not harmful. Infections frequently clear up if they are limited to small areas of the lung, but if they spread, they can progress very quickly and become life threatening.
- Lung damage over time can lead to obstruction in the airways in lungs, causing asthma-like conditions.

Initial Management. Acute chest syndrome can be fatal and must be treated immediately. Basic treatments include the following:

- Supplementary oxygen -- this is critical and life saving)
- Administration of fluids --overhydration should be avoided to reduce the risk of fluid in the lungs
- Pain relievers
- Bronchoscopy to identify infection --a diagnostic procedure involving insertion of a tube into the lower airways

Other Treatments. Other treatments include:

- High-dose intravenous corticosteroids (usually dexamethasone) may hasten recovery from acute chest syndrome and reduce the duration of hospitalization. They are also important if fat embolisms develop.
- Bronchodilator therapy uses drugs to open airways. It can be effective for some patients who are wheezing or have obstructed lung function.

- Antibiotics that specifically target the organisms (e.g., *Chlamydia*, *Mycoplasma*) that commonly trigger acute chest syndrome. Such antibiotics include erythromycin, azithromycin, clarithromycin, and various tetracyclines.

Transfusions. These are important early on for rapid improvement in severe cases, especially if fat embolisms have developed.

Use of Incentive Spirometry

To increase oxygen levels in children hospitalized for acute chest syndrome, a simple breathing technique known as incentive spirometry may be beneficial. A spirometer is a hand-held plastic device commonly used by asthma patients to measure their lung capacity and by patients after surgery to increase intake of oxygen. In one trial, children with sickle cell disease were asked to inhale and exhale into this device every 2 hours during the day and when they were awake at night until their chest pain subsided. This device forces more air into the lungs, and researchers hoped it would prevent the serious drop in oxygen levels and the risk for infection caused by acute chest syndrome. Results were encouraging. Children who used spirometry had significantly lower rates of collapsed lung tissue and infections than those who did not. This very inexpensive and simple treatment might have beneficial long-term effects.

Pneumonia and Other Infections

Infections are common and an important cause of severe complications in sickle cell patients. Before early screening for sickle cell disease and the use of preventive antibiotics in children, 35% of sickle cell infants were lost to infections. Fortunately, with screening tests for sickle cell now required for newborns in most states and with the use of preventive antibiotics in babies who are born with the disease, this terrible mortality rate has dropped significantly.

Infections in Infants and Toddlers with Sickle Cell Disease. The most common organisms causing infection in children with sickle cell disease are the following:

- *Streptococcus pneumoniae* (can cause blood infections or meningitis)
- *Haemophilus influenza* (a cause of meningitis)

Such infections pose a grave threat to infants and very young children with sickle cell disease. They can progress to fatal pneumonia with devastating speed in infants, and death can occur only a few hours after onset of fever. The risk for pneumococcal meningitis, a dangerous infection of the central nervous system, is also significant.

Infections in Children and Adults. Infections are also common in older children and adults with sickle cell disease, particularly respiratory infections such as pneumonia, kidney infections, and osteomyelitis, a serious infection in the bone. The organisms causing them, however, tend to differ from those in young children. The incidence of pneumococcal infections decrease and those caused by other bacteria increase, including the following:

- *Chlamydia* and *Mycoplasma pneumoniae*. These are the important infections in acute chest syndrome (*see above*).
- Gram-negative bacteria. This group of bacteria mostly infects hospitalized patients and can cause serious pneumonias and other infections.

General Approach to Treating Infections. Fever in any sickle cell patient should be considered an indication of infection. Temperatures over 101 F in children warrant a call to the doctor. Adults with sickle cell should call the doctor if they have a fever over 100 F and any signs of infection including chest

pain, productive cough, urinary problems, or any other symptoms. Some approaches for treating infections are as follows:

- Hospitalization for infections. When sickle cell patients develop infections, they are nearly always hospitalized immediately and treated with intravenous or high dose injections of antibiotics in order to prevent *septicemia*, the dangerous spread of the infection throughout the body. Antibiotics called cephalosporins (e.g., cefotaxime [Claforan], ceftriaxone [Rocephin] or cefuroxime [Ceftin]) are typically used. Repeated hospitalizations are very disruptive for both children and adults. Studies have found that older children whose fever is below 38.5 C (101 F) and who have no serious infection or other complications may not need hospitalization. Children who have indications of serious complications of infection (higher fevers, pain, a history of pneumonia, and signs of dehydration) should remain in the hospital.
- Treatment of osteomyelitis. If osteomyelitis, an infection in the bone, occurs, a 6-week antibiotic course is needed, most of it intravenous. An accurate diagnosis of osteomyelitis is sometimes difficult to make, because bone damage from sickling can cause similar symptoms. It should be strongly considered in children with signs of pain and swelling in the legs, a high white blood cell count, high fever, and high levels of a test that measures so-called sedimentation rates. It is important, however, to confirm the presence of an actual infection before administering antibiotics, because the antibiotic treatment required for osteomyelitis is so intensive and prolonged. The most common cause of osteomyelitis in children is *Salmonella*.
- Treatment of urinary tract infections. Urinary tract infections may be difficult to manage and can be a serious problem for pregnant women with sickle cell disease. Doctors should take a urine culture before beginning antibiotic treatment and another culture 1 to 2 weeks after treatment to be sure the infection has cleared up.

Using Antibiotics for Prevention. Preventive (prophylactic) antibiotics are the best approach for protection against pneumonia and other serious infections among children with sickle cell disease. Children diagnosed with sickle cell are given daily antibiotics, usually penicillin, unless a child is allergic and then alternatives are available. The ideal age for stopping preventive antibiotics is not yet clear, although the risk for serious infections are relatively lower in children older than 5 years of age.

Unfortunately, studies suggest that children who are on public medical insurance often receive inadequate treatment. In addition, many patients stop taking their antibiotics or the parents stop giving them to their children. Doctors are also concerned about developing bacterial resistance to common antibiotics and researchers warn that patients might experience breakthrough infections as resistance becomes more frequent.

Vaccinations. Everyone with sickle cell disease should have complete regular immunizations against all common infections. Children should have all routine childhood vaccinations. The following are important for everyone with sickle cell disease:

- Vaccination against *Haemophilus influenzae*, the major cause of childhood meningitis.
- Flu (influenza) vaccines should be received every winter.
- Pneumococcal vaccine. All sickle cell patients should be vaccinated with the pneumococcal vaccine. Protection lasts for over 6 years in most people. Children with sickle cell disease should receive 3 doses of the pneumococcal conjugated vaccine (Prevnar) between 2 and 6 months of age, followed by 2 doses at age 1 and then vaccinations at age two, 5, and every 10 years afterward. (Some experts recommend every 5 years rather than every 10 years.)

- Tuberculosis test every year.
- Hepatitis B vaccine. Anyone starting transfusion therapy should receive this vaccine if they had not been immunized as children.

Other Effects on the Lungs

Impaired Lung Function. A 2003 study observed impaired lung function starting at very early ages (5 years and older) in children with sickle cell. Although not outside the normal range, such signs of abnormalities in the airways of the lungs may warrant early treatments for obstructive or restrictive lung disease (which are similar to those for asthma patients).

Pulmonary Hypertension. Pulmonary hypertension is a serious condition that develops if blood pressure in the lungs increases, in some cases to a dangerous level. Research published in 2004 in the *New England Journal of Medicine* confirmed that it is an important and often unrecognized complication and cause of death in sickle cell disease. Based on the evidence, the researchers urged that all adults with sickle cell disease undergo echocardiographic testing to identify and treat those patients at highest risk. The primary symptom is shortness of breath, which is often severe. Pulmonary hypertension can be very serious and life threatening in the short- and long-term. If pulmonary hypertension develops suddenly it can cause respiratory failure, which is life threatening. Over time, pulmonary hypertension may cause a condition called *cor pulmonale*, in which the right side of the heart increases in size. In some cases, this enlargement can lead to heart failure. Bosentan (an endothelin receptor antagonist), and other drugs are used to treat this condition. Investigative therapies include nitric oxide, L-arginine (which converts to nitric oxide), blood transfusions, warfarin, vasodilators, and sildenafil (Viagra). Hydroxyurea does not appear to be effective for treating sickle cell associated pulmonary hypertension.



Click the icon to see an image of cor pulmonale.

Stroke

After acute chest syndrome, stroke is the most common killer of patients with sickle cell disease who are older than 3 years old. Between 8 - 10% of patients suffer strokes, typically at about age 7. Transfusions are proving to prevent a first stroke as well as recurrence. Strokes are usually caused by blockages of vessels carrying oxygen to the brain. Patients with sickle cell disease are also at high risk for strokes caused by aneurysm, a weakened blood vessel wall that can rupture and hemorrhage. Multiple aneurysms are common in sickle cell patients, but they are often located where they can be treated surgically. (Some experts believe that any patient who has neurologic symptoms indicating a potential stroke should undergo angiography, an invasive diagnostic technique useful for detecting aneurysms.)



Click the icon to see an image of stroke.

Transfusions for Prevention of Stroke. Compelling data show that regular (every 3 to 4 weeks) blood transfusions can reduce the risk of a first stroke by 90% in high-risk children. The objective of such transfusions is to reduce hemoglobin S concentrations to less than 30% of total hemoglobin. Studies

indicate that as many as 90% of patients who have experienced a stroke do not experience another stroke after 5 years of transfusions.

In December 2004, the National Heart, Lung, and Blood Institute (NHLBI) issued a clinical alert strongly advising doctors against terminating regular transfusions for high-risk children. The alert was based on data from the Stroke Prevention Trial II (STOP II) that was presented at the the American Society of Hematology annual conference. STOP II assessed if children with sickle cell anemia who were at high risk for stroke could safely stop receiving preventive blood transfusions after a minimum of 30 months. The trial was halted early due to compelling evidence that transfusion cessation significantly increased the risk for stroke.

Chronic blood transfusions carry their own risks including iron overload, alloimmunization (an immune response reaction), and exposure to bloodborne pathogens. Still, the STOP II trial data suggest that the risks for stroke outweigh the risks associated with transfusions. Researchers are working on ways to reduce the side effects associated with transfusion treatment.

Unfortunately, no tests can definitely determine which individual children are at highest risk for a first stroke and, therefore, would be candidates for ongoing transfusions. The following are diagnostic tools currently used or under investigation:

- Transcranial Doppler (TCD) ultrasonography measures the speed of blood flow in the brain and is the most sensitive method to date for identifying children at risk for stroke. However, the results of the STOP II trial indicated that high-risk children were still vulnerable to stroke even if the TCD screening diagnosed normal blood flow velocities.
- The use of follow-up magnetic resonance imaging (MRI) to detect small blockages in blood vessels may help confirm high risk in patients identified by TCD ultrasound. A 2001 study indicated that giving transfusion therapy to children who showed abnormalities after an MRI reduced the risk for stroke.
- Researchers are also beginning to uncover possible genetic markers that may eventually be used to help identify sickle cell patients at higher risk for stroke.

Until diagnostic tests can be more precise, or effective alternative treatments to transfusions exist, patients and their caregivers and doctors must make the best decisions they can.

Anticoagulants. Researchers have investigated anti-blood clotting drugs such as aspirin and heparin for preventing stroke. However, their use is controversial, and their effects on children are unclear and understudied.

Anemia

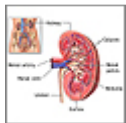
Anemia is a significant characteristic in sickle cell disease (which is why the disease is commonly referred to as sickle cell anemia).

Hemolytic Anemia and Aplastic Crises. Because of the short life span of the sickle red blood cells, the body is often unable to replace red blood cells as quickly as they are destroyed. This causes a particular form of anemia called hemolytic anemia. Episodes of hemolytic anemia are called *aplastic crises*, which are usually managed well with transfusions. In about 80% of cases, aplastic crises are triggered by a virus called human parvovirus B19. There is some evidence that the virus increases the risk for neurologic complications, including encephalitis and stroke. (This virus is common and usually harmless in healthy individuals.)

Chronic Anemia. Chronic anemia reduces oxygen and increases the demand on the heart to pump more oxygen-bearing blood through the body. Eventually, this can cause the heart to become dangerously enlarged, with an increased risk for heart attack and heart failure. Folic acid and possibly iron supplements are often given to help treat the anemia that occurs in patients with sickle cell disease. (Patients who are given multiple transfusions may experience iron overload, and iron supplements should be avoided in such cases. Also of note, folic acid can mask pernicious anemia, which is caused by deficiency of vitamin B12 and is more common in African Americans than other populations.)

Problems in the Kidney

The kidneys are particularly susceptible to damage from the sickling process. Persistent injury can cause a number of kidney disorders, including infection. Problems with urination are very common, particularly uncontrolled urination during sleep. Patients may have blood in the urine, although this is usually mild and painless and resolves without damaging consequences. Kidney failure is a major danger in older patients and accounts for 10 - 15% of deaths in sickle cell patients. Renal medullary carcinoma is an aggressive, rapidly destructive tumor in the kidney that is rare but can occur as a result of sickle cell.



Click the icon to see an image of kidney anatomy.

Treatment for Kidney Problems. Kidney damage in sickle cell patients can cause bleeding into the urine. Mild episodes can usually be treated with bed rest and fluids. Severe bleeding may require transfusions. ACE inhibitors are drugs commonly used to control high blood pressure and are proving to be important for preventing hypertension and kidney failure in sickle cell patients. Such drugs include captopril (Capoten), enalapril (Vasotec), quinipril (Accupril), benazepril (Lotensin), and lisinopril (Prinivil, Zestril).

Problems in the Genital Tract

A reported 38 - 42% of males, including children, with sickle cell disease suffer from priapism. Priapism causes prolonged and painful erections. Experts think that priapism in sickle cell disease may be caused by the destruction of red blood cells and subsequent reduction of nitric oxide. If priapism is not treated, partial or complete impotence can occur in 80% of cases.

Treatment for Priapism. Priapism, prolonged and sometimes painful erections, must be treated to prevent partial or complete impotence, which can result from erections that last several hours to days. Exchange transfusions may be used to reduce the hemoglobin S and sickling that cause this condition. Drugs used to prevent priapism include terbutaline and phenylephrine, which help restrict blood flow to the penis. Hormonal treatments such as leuprolide (Lupron) and diethylstilbestrol may prevent repetitive and prolonged episodes of priapism in severely affected teenage boys with sickle cell disease. A surgical procedure that implants a shunt to redirect blood flow is sometimes performed. Inflatable penile implants may help maintain potency without causing priapism. Researchers are also investigating other treatments including inhaled nitric oxide, arginine, and sildenafil (Viagra).



Click the icon to see an image of the male reproductive anatomy.

Problems in the Liver

Enlargement of the liver occurs in over half of sickle cell patients, and acute liver damage occurs in up to 10% of hospitalized patients. Because sickle cell patients often need transfusions, they have been at higher risk for viral hepatitis, an infection of the liver. This risk, however, has decreased since screening procedures for donated blood have been implemented.



Click the icon to see an image of cor pulmonale.

Gallbladder Disease

About 30% of children with sickle cell disease have gallstones, and by age 30, 70% of patients have them. In most cases, gallstones do not cause symptoms for years. When symptoms develop, patients may feel overly full after meals, have pain in the upper right quadrant of the abdomen, or have nausea and vomiting. Acute attacks can be confused with a sickle cell crisis in the liver. Ultrasound is usually used to confirm a diagnosis of gallstones.

Treatment of Gallbladder Disease. Children with sickle cell disease have an increased risk for gallstones. However, if they have no symptoms, no treatment is usually necessary. If they have recurrent or severe pain from gallstones, the gallbladder may need to be removed. Minimally invasive procedures (using laparoscopy) reduce possible complications. [See *In-Depth Report #10: Gallstones.*]



Click the icon to see an image of cholithiasis.

Damaged Spleen

The spleen of most adults with sickle cell anemia is nonfunctional due to recurrent episodes of oxygen deprivation that eventually destroys it. Injury to spleen causes abnormalities in immune function and increases the risk for serious infection. A very serious anemic condition called *acute splenic sequestration* crisis (sudden spleen enlargement) can occur if the damaged spleen suddenly enlarged from trapped blood.

Treatment for Complications in the Spleen. The spleen is often removed (splenectomy) in children who have one or two acute splenic sequestration crises. Transfusion therapy is an alternative for preventing acute splenic sequestration in high-risk patients. At this time there are no studies comparing overall survival and benefits between the two approaches.



Click the icon to see an image of an enlarged spleen.

Problems in the Bones and Joints

In some children with sickle cell disease, excessive production of blood cells in the bone marrow causes bones to grow abnormally, resulting in long legs and arms or misshapen skulls. Sickling that blocks oxygen to the bone can also cause bone loss and pain. Sickling that affects the hands and feet of children causes a painful condition called hand-foot syndrome. A condition called avascular necrosis of the hip occurs in about half of adult sickle cell patients when oxygen deprivation causes tissue death in the bone. Eventually adult patients may require surgery to remove diseased and dead bone tissue. Joint replacement may be required in severe cases. X-rays are not very useful for detecting early disease in the bones. MRI may be important. Ultrasound is also a helpful tool in diagnosing and treating these abnormalities.



Click the icon to see an image of the blood supply to bone.

Leg Sores and Ulcers

Leg sores and ulcers occur in up to 10% of sickle cell patients and usually affect patients older than 10 years. They are difficult to treat, and, at this time, simple treatment with a moist dressing provides the best results. To treat mild ulcers, the leg should be gently washed with cotton gauze soaked in mild soap or a solution of one tablespoon of household bleach to one gallon of water. A dressing soaked in diluted white vinegar may be applied every three to four hours.

More severe ulcers require debridement, which is the removal of injured tissue until only healthy tissue remains. Debridement may be accomplished using chemical (enzymes), surgical, or mechanical (e.g. irrigation) means. Hydrogels (Nu-Gel, Intrasite Gel, Scherisorb, Clearsite, Duoderm, Geliperm) are helpful in healing ulcers and are noninvasive and soothing. Topical antibiotics, saline or zinc oxide dressings, or cocoa butter or oil are also used depending on severity. The leg should be elevated and bed rest for a week or more is sometimes required for severe ulcers.

Skin grafts and transfusions have been helpful in some extreme cases. In a promising 2002 study administering arginine butyrate for many weeks improved ulcer healing by ten-fold. (This drug is also under investigation for other beneficial effects in sickle cell patients.)

Neurological Complications

In one 2000 study of adults with sickle cell disease, 22% suffered from neurologic complications. Stroke is a major factor in such problems. Sickle cell disease also poses a high risk for mild mental deficiency from low levels of oxygen in brain tissue or from silent strokes, even in the absence of a major stroke. Such deficiencies can impair learning and behavior but may not even show up on normal imaging tests and thus may not be attributed to sickle cell disease. Some experts recommend clinical trials using brain scans to detect the location of small injuries and try to determine whether they might be causing mental or behavioral problems that are inaccurately believed to be unrelated to the disease.

Pregnancy and Sickle Cell Disease

Women with sickle cell disease who become pregnant are at higher risk for complications, but serious problems have dropped significantly over the past decades. A 2001 study reported a higher risk for premature birth and low birth weight in the baby, and a higher risk for infections and hospital visits in the mother after delivery. Pain crises occur in nearly half of women and nearly 60% required transfusions.

The study also reported, however, that, in general, the outcome for pregnancy is favorable. Still, pregnancy during sickle cell is high-risk and carries a mortality rate of about 1%.

Treatment During Pregnancy. Women who are pregnant should be treated at a high-risk clinic. They should take folic acid in addition to multivitamins and iron. Standard treatment is given for sickle cell crises, which may occur more frequently during pregnancy. The benefits of transfusions to prevent crises during pregnancy are not yet clear and experts recommend them only for women who experience frequent complications during pregnancy.

Other Medical Complications

Older children and adult patients with sickle cell are subject to other medical problems, including impaired physical development, gum disease, and scarring and detachment of the retina.

Treatment

Research is ongoing toward identifying the biologic and chemical activities that promote or protect against the sickle cell process. Currently, experimental treatments focus on the basic processes that cause the red blood cells to sickle in the first place. There are three basic modes of treatment:

- Stimulation of production of healthy fetal hemoglobin in order to inhibit the sickling process.
- Blocking dehydration in the cells.
- Transplantation of bone marrow or stem cells from healthy donors so that normal hemoglobin is produced rather than hemoglobin S.

Drugs that Stimulate Fetal Hemoglobin

Hemoglobin F (HbF, also called fetal hemoglobin) is the form of hemoglobin that exists in the fetus and small infants. Most HbF is later replaced by the hemoglobin that is present in the growing child and adult, although some HbF may persist. Fetal hemoglobin is able to block the sickling action of red blood cells so that infants with sickle cell disease do not develop symptoms of the illness while they still have hemoglobin F. Adults who have sickle cell disease but still retain high levels of hemoglobin F generally have mild disease.

Studies are now reporting that the severity of sickle cell disease can be reduced by using drugs that stimulate production of HbF. Even increases as modest as 4% may have a significant benefits for these patients.

Hydroxyurea. Hydroxyurea (Droxia, Hydrea) destroys cells in the bone marrow, which results in an increase in special cells that can produce HbF. It is currently the only drug in general use to prevent acute sickle cell crises. It appears to have a number of effects on sickle cell:

- Hydroxyurea reduces the intensity and frequency of sickle cell crises by nearly 50%. (It does not have any effect on pain, however, once it starts.)
- Over time, the drug may improve spleen function, which aids in the immune process, particularly in children.
- Hydroxyurea increases water content in red blood cells.
- The drug reduces the number of neutrophils, the white blood cells that contribute to the process causing sickle cells to stick to the blood vessel walls. This effect may actually be more protective over time than its effect on increasing levels of hemoglobin F.

Hydroxyurea is now indicated in adults and adolescents with moderate to severe recurrent pain (occurring three or more times a year). The drug is proving to reduce sickling crises and pain, priapism, the number of transfusions, and life-threatening complications in this group. The benefits appear to be long lasting.

For example, a 2002 study reported that after 4 years patients who had taken the drug for at least 2 years experienced 30% fewer hospitalizations and 58% fewer transfusions than before they took hydroxyurea. In a 9-year study, the drug also reduced mortality rates by about 40%. Hydroxyurea is not a cure-all. Not all patients respond to hydroxyurea, and the best candidates for the treatment are not yet clear. Small studies have reported no protection from damage in the spleen or bones and joints. Effects on stroke and complications in the eye or kidney are not yet known.

Hydroxyurea is still being investigated in young people. To date, the response to the drug in children and teenagers with sickle cell disease is similar to the response in adults, and few severe adverse effects are being reported. Recent research also suggests that hydroxyurea is safe and beneficial for infants. A 2005 study indicated that long-term hydroxyurea treatment can improve height, weight, and spleen function, and reduce episodes of acute chest syndrome. Patients in the study started the treatment as babies, and most patients took the drug for at least 4 years. The drug was given by mouth in a flavored liquid form.

Side effects include gastrointestinal problems, headache, drowsiness, and skin and nail changes. In rare cases, there have been reports of hallucinations and seizures. Long-term use of hydroxyurea (three years) may induce leg ulcers in certain patients. There is some concern that it may also pose a slight long-term risk for cancers, such as leukemia, but long-term research is needed. At this time, it should not be used during pregnancy.

Cytidine Analogues. Cytidine analogues increase HbF production by affecting the genes that regulate it. Decitabine is one such drug that was developed to treat leukemia and other blood malignancies. Early studies are suggesting that it significantly increases HbF production, even in patients who have failed hydroxyurea. Only minor toxic side effects have been reported to date.

Butyrates. Butyrates are natural fatty acids, which are the end-products of fermented carbohydrates in the intestinal tract and they are also metabolized from fiber. One derivative, arginine butyrate, has been under investigation for some time in sickle cell for its role in stimulating production of HbF. Intermittent therapy using intravenous administration has achieved increased levels. In a promising 2002 study administering arginine butyrate improved ulcer healing by ten-fold. Because its actions are different from hydroxyurea, experts hope the two drugs may eventually be used in combination. However, arginine butyrate is difficult to administer, and experts are looking for different forms that might make it simpler to use.

Nitric Oxide and Arginine

Nitric oxide, a soluble gas, is a natural chemical in the body that relaxes smooth muscles and expands blood vessels. Hemoglobin removes nitric oxide. Because sickle cells release hemoglobin, patients with the disease are deficient in nitric oxide. This lack of nitric oxide constricts blood vessels and causes pain in sickle cell diseases. In adult patients, men may be more susceptible to this effect than women. Some studies indicate that inhaling nitric oxide may slow the disease process and improve symptoms in acute sickle cell crises. It is difficult to administer, however. (Nitric oxide is not the same substance as nitrous oxide, the so-called laughing gas used in dentistry.)

Sickle cell disease can cause red blood cells to break apart. This process is called hemolysis. Hemolysis causes a lack of the amino acid arginine. Arginine is involved in producing nitric oxide. Recent research suggests that a lack of arginine may contribute to the development of pulmonary hypertension, a leading cause of death in patients with sickle cell disease. Pulmonary hypertension causes high blood pressure in the arteries that carry blood to the lungs.

A 2005 study found that patients with sickle cell who had low levels of arginine were 3.6 times more likely to die than patients with high arginine levels. Most patients in the study died from pulmonary hypertension. Scientists are working on developing a blood test that could measure amino acid levels and help identify patients at greatest risk of death. They are also working on developing drugs that could block arginase, a protein in cells that is released during hemolysis, which consumes arginine. Doctors are not yet sure whether arginine nutritional supplements are helpful or harmful for patients with sickle cell disease. Patients should talk to their doctor before taking these or other supplements.

Drugs to Prevent Dehydration

Researchers are studying the mechanisms behind cell membrane damage, dehydration, and potassium loss in order to develop drugs that will inhibit these processes. Promising drugs under investigation are those that specifically block the Gardos channel, which is an important route for potassium loss and dehydration. They include magnesium pidolate and clotrimazole and its derivatives.

Clotrimazole. Clotrimazole (a common ingredient in ointments such as Lotrimin or Mycelex, which are used to treat fungal skin infections) stops potassium from leaving and calcium from entering red blood cells. This prevents water loss in the cells. Early studies using an oral form of clotrimazole have been promising, but more research is needed.

Magnesium. Small studies have reported some benefits from the use of supplements containing magnesium pidolate to improve potassium and calcium interactions. A trial is currently underway.

Zinc. Zinc sulphate appears to help reduce red blood cell dehydration. Important studies are reporting that it helps prevent sickle cell crises and reduce pain and life-threatening complications.

Piracetam. Piracetam (Nootropil) prevents water loss, and important studies suggest that it may reduce sickle cell crises and pain. It also may improve rehabilitation in people who have had strokes.

Bone Marrow or Stem Cell Transplantation

The only true cure for sickle cell disease at this time is bone marrow or stem cell transplantation. The bone marrow nurtures stem cells, early cells that mature into red and white blood cells and platelets. By destroying the sickle cell patient's diseased bone marrow and stem cells and transplanting healthy bone marrow from a genetically matched, or allogeneic, donor, normal hemoglobin may be produced. Trials using a few carefully selected patients have reported very successful results.

Candidates. Possible candidates for transplantation are patients with the following conditions:

- A history of stroke
- Sickle pulmonary disease
- Recurrent acute chest syndrome or vaso-occlusive crises

Up to 80 - 85% of patients who receive transplants remain disease free. Unfortunately, only about 7% meet the criteria for transplantation, which include:

- Age 16 or younger
- Severe symptoms but no long-term organ or neurologic damage
- Presence of genetically matched brother or sister who will donate their marrow

Complications. Bone marrow transplant carries its own dangers and limitations. About 10% of those treated die from the treatment. Some complications include:

- Transplanted cells which come from a donor (called allogeneic grafts) may attack the patient's own tissues, a potentially fatal condition called graft-versus-host disease (GVHD). Drugs that destroy bone marrow and suppress immunity must be administered before the procedure so that the body's immune system does not attack the transplanted tissue. Nonetheless, this does not always prevent the problem.
- Other very serious complications include bleeding, pneumonia, and severe infection.
- Those who live but are not cured face long-term problems caused by the drugs used in transplantation and by the disease itself.
- Even in those who are cured, long-term consequences may include a higher risk for cancer and infertility.

Investigative Approaches. Experts hope that better diagnostic techniques will identify at an early age more patients who are at high risk for developing serious sickle cell disease and in whom the benefits of transplantation would outweigh the risks. Researchers are also investigating regimens that might be suitable for adult patients and less toxic regimens.

The use of umbilical cord blood and cells from placentas is showing promise for providing healthy stem cells to patients who do not have genetically matched donors for bone marrow transplant. Cord blood has certain advantages over stem cell transplantation, including the capacity to produce more cells quickly. Because immune factors in cord blood are immature, the risk and severity of graft-versus-host disease (GVHD) may be reduced.

Early trials are also reporting some success with a process called partial chimerism, in which a mixture of the patient's and a donor's bone marrow is used. The procedure has far fewer side effects because all the bone marrow is not destroyed. Although some sickle blood cells remain, small studies indicate that the patients are still free of the typical infections and pain of the disease.

Transfusion Therapy in Sickle Cell Disease

Transfusions are often critical for treating sickle cell disease. In some cases they may be given on a regular basis to prevent stroke or other life-threatening complications of the disease. Ongoing transfusions can reduce episodes of pain and acute chest syndrome. They can also help improve height and weight in children with sickle cell disease. Regular transfusions, however, can have severe side effects.

Transfusions are may required by sickle cell patients either for specific episodes (used only for specific events) or as chronic transfusions (ongoing transfusions).

Episodic Transfusions. Episodic transfusions are needed in the following situations:

- To manage sudden severe events, including acute chest syndrome, stroke, widespread infection (septicemia), and multi-organ failure.
- To manage severe anemia, usually caused by splenic sequestration (dangerously enlarged spleen) or aplasia (halting of red blood cell production, most often caused by parvovirus). Transfusions are generally not required for mild or moderate anemia.
- Before major surgeries. Some evidence suggests that a conservative transfusion regime is as effective as aggressive transfusions in these cases, but more research is needed. Transfusions are generally not required for minor surgeries.

Chronic Transfusions. Chronic transfusions are used in patients who have:

- Pulmonary hypertension and chronic lung disease

- Heart failure
- Chronic kidney failure and severe anemia
- Unusually severe and protracted episodes of pain

Transfusions are also used to prevent first or recurrent strokes. An important study confirmed previous work that shows chronic transfusions reduce the risk for stroke in children by over 90%.

Kinds of Transfusions. Transfusions may be either simple or exchange.

- **Simple Transfusion.** Simple transfusions involve the infusion of one or two units of donor blood to restore blood volume levels and oxygen flow. It is used for moderately severe anemia, severe fatigue, and nonemergency situations when there is a need for increased oxygen. It is also used for acute chest syndrome.
- **Exchange Transfusion.** Exchange transfusion involves drawing out the patient's blood while exchanging it for donor red blood cells. It can be done as manual procedure or as automatic one called erythrocytapheresis. Exchange transfusions should be used promptly if there is any evidence that the patient's condition is deteriorating. It prevents stroke and also may be used in patients with severe acute chest syndrome and to reduce the risk of iron overload in patients who require chronic transfusion therapy. Other indications are not fully defined. Studies suggest that it may improve oxygenation and reduce hemoglobin S levels. Exchange transfusion may also reduce the risk of heart failure and help prevent fat embolism, a life-threatening condition in which fatty tissue from the bone marrow travels to blood vessels in the lungs and cuts off oxygen.

Iron Overload and Chelation Therapy. Iron overload increases risk for complications including liver cancer and heart failure. A liver biopsy accurately determines whether excess iron levels are present. A non-invasive test called a superconducting quantum interference device (SQUID) should be used if available.

Chelation therapy is used to remove excess iron stores in the body that can harm the liver, heart, and other organs. The drug deferoxamine (Desferal) is commonly used during such therapy. Unfortunately, deferoxamine has some severe side effects and must be used with a pump for about 12 hours each day. Many patients do not continue treatment. In 2005, the drug deferasirox (Exjade) was approved for the treatment of transfusion-related iron overload in patients ages 2 and older. It is taken once a day by mouth. Patients mix the pills in liquid and drink the mixture. This new treatment may make chelation therapy much easier and less painful for patients.

Other Complications of Transfusion Therapy.

- **Immune reactions.** An immune reaction may occur in response to donor blood. In such cases, the patient develops antibodies that target and destroy the transfused cells. This reaction, which can occur five to 20 days after transfusion, can result in severe anemia and may be life threatening in some cases. It can be generally prevented with careful screening and matching of donor blood groups before the transfusion.
- **Hyperviscosity.** With this condition, a mixture of hemoglobin S and normal hemoglobin caused the blood to become sticky. The patient is at risk for high blood pressure, altered mental status, and seizures. Careful monitoring can prevent this condition.
- **Transmission of viral illness.** Before widespread screening, transfusions were highly associated with a risk for hepatitis and HIV. This complication has decreased considerably.

Lifestyle Changes

There are no proven methods for preventing either sickle cell crises or long-term complications of sickle cell disease. By taking precautions and aggressively managing problems that occur, however, patients are now living longer with a better quality of life.

General Precautions

To prevent or reduce the severity of long-term complications, a number of precautions may be helpful that include the following:

- Have regular physical examinations every three to six months.
- Have periodic and careful eye examinations.
- Have sufficient rest, warmth, and increased fluid intake. (These are critical precautions for reducing oxygen loss and the risk for dehydration.)
- Avoid conditions, such as crowds, that increase risk for infections.
- Avoid excessive demands on the body that would increase oxygen needs (physical overexertion, stress). Low impact exercise (leg lifts, light weights) may be useful and safe for maintaining strength, particularly in the legs and hips, but patients should consult their doctor about any exercise program.
- Avoid high altitudes if possible. If flying is necessary, be sure that the airline can provide oxygen.
- Do not smoke, and avoid exposure to second-hand smoke. Both active and passive smoking may promote acute chest syndrome in sickle cell patients.

Dietary Factors and Supplements

Foods. Good nutrition is essential for anyone and critical for patients with sickle cell disease. Some dietary recommendations are as follows:

- Fluids are number one in importance. The patient should drink as much water as possible each day to prevent dehydration. Female patients may want to include cranberry juice to help prevent urinary tract infections.
- It is important to have five to nine daily servings of green, red, and yellow vegetables, fruits, or juices that are rich in antioxidants and other important nutrients. Some research suggests that antioxidant foods or supplements (such as vitamins E or C) may help inhibit the formation of the dense cells that trigger a sickle cell crisis. One medical group has created a "cocktail" of supplements and food extracts that were rich in antioxidants and iron-binding compounds that might have more protective effects on the sickling process than single antioxidants. It includes garlic extract, black and green tea extract, pycnogenol, alpha-lipoic acid, vitamin E, coenzyme Q(10), and beta-carotene. In any case patients might eat foods containing these extracts and take supplements of the antioxidant vitamins E and C if their diet does not adequately supply them.
- The chemical resveratrol, which is found in red grape skins, appears to have properties similar to hydroxyurea, the primary drug used in sickle cell disease. Drinking great amounts of grape juice is unlikely to make much difference, but adding it to a child's diet is unlikely to do harm.
- Protein is important for sickle cell patients.
- Studies on omega-three fatty acids, found in fish and soybean oil, suggest that they might make red blood cell membranes less fragile, and possibly less likely to sickle, although no studies have proven this definitively. Fish and soy products have health benefits in any case.

In one study, fish oil supplements reduced the frequency of painful episodes in 10 sickle cell patients over the course of a year compared to those given olive oil capsules.

Minerals and Other Natural Substances.

- **Zinc.** Zinc sulphate appears to help reduce red blood cell dehydration. Important studies are reporting that it helps prevent sickle cell crises and reduce pain and life-threatening complications. A study on children with sickle cell suggested that supplements may help improve growth and weight gain. It may also boost the immune system and help protect against bacterial infections. Zinc deficiency is a common nutritional problem in sickle cell disease, so supplements may be important.
- **Magnesium.** Magnesium protects against potassium and water loss in sickle cells. Small patient studies are reporting promise for its use in preventing dehydration and increases in the hemoglobin S concentration.
- **Arginine.** Arginine is an amino acid that the body converts to nitric oxide, a natural substance that relaxes blood vessels. The sickle cell process reduces nitric oxide levels, which may be responsible for much of the pain in these patients. Arginine and other substances that convert to nitric oxide are being studied in trials.
- **L-glutamine** is an ordinary amino acid that is heavily used by sickle cells. One study using supplements of this substance reported that after a month it caused changes in the blood that might prove to have benefits for sickle cell patients. Another small study found that daily oral glutamine supplementation improved growth and nutritional measures in children and adolescents with sickle cell anemia.

Vitamins. Patients should take daily folic acid and vitamin B12 and B6 supplements. All are important for reducing homocysteine levels, a risk factor in general for heart disease and which may be particularly damaging in sickle cell patients. Vitamin B6 may have specific anti-sickling properties. Some experts recommend 1 mg folic acid, 6 microgram vitamin B12, and 6 mg vitamin B6. Foods containing one or all of these vitamins include meats, oily fish, poultry, whole grains, dried fortified cereals, soybeans, avocados, baked potatoes with skins, watermelon, plantains, bananas, peanuts, and brewer's yeast. Of note, folic acid can mask pernicious anemia, which is caused by deficiency of vitamin B12 and is more common in African Americans than other populations.



Click the icon to see an image of vitamin B6 sources.

Note on Iron. Although sickle cell disease is often referred to as anemia, iron supplements or iron rich foods should be avoided in patients receiving multiple transfusions, which increase the risk for iron-overload.

Relief for Mild Pain

For mild pain relief, common medications such as acetaminophen (Tylenol) or the class of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs) are often sufficient. Aspirin is the most common NSAID, but there are many others, including ibuprofen (Advil, Motrin) and naproxen (Naprosyn, Aleve). Aspirin is not usually recommended for children because it can aggravate abdominal pain.

Managing the Emotional and Social Impact

In assessing the seriousness of this disease, no one should underestimate its emotional and social impact. For the family, there is nothing more heartbreaking than to watch their child endure extreme pain and life-threatening medical conditions. The patient endures not only the pain itself but also the emotional strain from unpredictable bouts of pain, fear of death, and lost time and social isolation at school and work. Academic grades among patients average less than C, even in children with a low frequency of hospitalization (averaging 17 days a year).

These problems continue over the years, and both children and adults with sickle cell disease often suffer from depression. The financial costs of medical treatments combined with lost work can be very burdensome.

Any chronic illness places stress on the patient and family, but sickle cell patients and caregivers often face great obstacles in finding psychological support for the disease. Communities in which many sickle cell patients live generally lack services that can meet their needs, and professionals who work in their medical facilities are often overworked. In a study comparing patients with different kinds of long-term illnesses, those with sickle cell disease gave the lowest scores to their doctors and other professional caregivers for compassion and satisfaction with medical care.

It is very important for patients and their caregivers to find emotional and psychological support. No one should or can endure this life-long disease alone. Unfortunately, studies indicate that most patients do not receive even basic supportive care that could help reduce the anxiety and intensity of pain that occurs when a sickle cell crisis erupts.

The following are some measures that some people find helpful in dealing with this disease.

- *Stress Reduction.* Stress reduction techniques and relaxation methods appear to be helpful. Those that use breathing and mediation techniques may be very helpful.
- *Cognitive-Behavioral Therapy.* Studies suggest that cognitive behavioral therapies that teach coping skills can result in less negative thinking and even less pain. Coping skills refer to the patient's ability to respond to symptoms, such as pain. Some patients cope best with many active efforts (keeping warm, replacing fluids) after taking pain medication. Other preferred withdrawing and resting until the medication became effective.
- *On-Line Support Help.* Computer on-line services are now valuable sources of support groups and access to research. They are particularly valuable for patients who cannot easily leave home or for patients who are ill. Computers and the monthly charges for on-line services are still costly, however.
- *Support Associations.* Parent and professional support associations still offer the best and least expensive sources of help.

Other factors that are important are those that help maintain positive attitudes, including spirituality, humor, or having important life goals (children, jobs, etc).