Sickle−Cell Disease

WHAT IS SICKLE−CELL DISEASE?

Hemoglobin and the Sickle−Cell Disease Process

Hemoglobin is a complex molecule and the most important component of red blood cells. [For a description of blood and the role of hemoglobin, *See Box* Blood.] Sickle−cell disease occurs from genetic abnormalities in hemoglobin:

- Normal red blood cells contain molecules called *hemoglobin A*.
- In a sickle red blood cell, a variant of this molecule exists and is called *hemoglobin S* (S for sickle).

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.

Polymerization and Other Changes in Hemoglobin S Leading to 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.
- These abnormally sickle−shaped cells are both rigid and sticky. They cannot squeeze through the capillaries, and so block the flow of blood, depriving tissues and organs of oxygen.
- 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 a 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 −− free from red blood cells −− are also released into the bloodstream. Free hemoglobin serves as a scavenger of nitric oxide, an important chemical that relaxes blood vessels. Eliminating nitric oxide can result in severe narrowing of blood vessels, which may turn out to be an important cause of the intense pain that occurs in sickle cells disease.
- 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.

Factors Determining Severity

A number of harmful effects occur as a result of the polymerization process. The severity of sickle−cell disease generally depends on a number of factors:

- *The extent of oxygen loss.* Prolonged oxygen deprivation contributes to both short− and long−term organ damage. The lungs supply the oxygen that can restore the sickle molecules to a normal form. Unfortunately, once they begin to lose oxygen, 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 molecule called hemoglobin F (for fetal).* The more the better. Hemoglobin F is produced in everyone during fetal development in the womb and for a short time after birth. Some hemoglobin F persists throughout life. In sickle−cell patients, hemoglobin F does not polymerize and form sickle−shapes, so its red blood cells continue to function normally. People with the sickle−cell gene who continue to carry some fetal hemoglobin are better protected, therefore, from severe forms of the disease.

BLOOD

Blood Components

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

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

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 and an iron−containing molecule called *heme*, which binds oxygen in exchange for carbon dioxide in the lungs. 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*, which is the power source within all cells.

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.

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

WHO GETS SICKLE−CELL DISEASE?

Populations at Risk for Sickle−Cell Disease and its Association with Malaria

Sickle−cell disease is inherited. People at risk for inheriting the gene for sickle cell are descended 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, although it is often a milder variant.

WHAT ARE THE SYMPTOMS OF SICKLE−CELL DISEASE?

General 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.
- Infants also may have nosebleeds and frequent upper respiratory infections.

General Symptoms in Childhood. After infancy, children develop the following symptoms:

- Pain is the most common complaint.
- Anemia.
- Fatigue.
- Irritability.
- Jaundice (yellowish discoloration of the skin and eyes).

General Symptoms in Adolescence. In adolescence and young adulthood, symptoms often also include the following:

- 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. Although they cannot be predicted, 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. 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. [For more information on Pain in the Acute Sickle−Cell Crisis *see* What Are the Complications of Sickle−Cell Disease and Their Treatments?]

HOW IS SICKLE−CELL DISEASE DIAGNOSED?

Prenatal Testing

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 physicians 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 physicians. 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.

Tests for Newborns

In 1987, the National Institutes of Health recommended that all newborns, regardless of country of origin or ethnic background, be tested for sickle−cell disease. Most states, though not all, now screen infants for the 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. If an infant is diagnosed with sickle−cell disease, the parents should be offered genetic counseling and information on the problem. Parents of at−risk children should note that transfusions prior to testing for sickle−cell disease can impair the detection of the disease.

Ruling Out Other Diseases

- part of the diagnosis, the physician 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.

HOW SERIOUS IS SICKLE−CELL DISEASE?

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.

Survival Rates

New and aggressive treatments for sickle−cell disease are prolonging life and improving its quality. As recently as 1960, most people with sickle−cell disease were not expected to survive childhood. Yet, a major 1994 study reported that 85% of children with full−blown sickle−cell disease and 95% of those with a less serious variation were living into adulthood. Currently, about half of sickle−cell patients live beyond 50 years. 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.

Complications over Time

Sickle−cell children are very susceptible to infections, usually because their damaged spleens are unable to protect the body from bacteria. As medical progress has increased the lifespan of children with sickle−cell disease, older patients are now facing medical problems related to long−term damage. In older children and adults, the most serious dangers are 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. Physicians are only recently developing ways to treat these complications effectively. [*See* What Are the Complications of Sickle−Cell Disease and Their Treatments?]

WHAT ARE THE COMPLICATIONS OF SICKLE−CELL DISEASE AND THEIR TREATMENTS?

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 in the Acute Sickle−Cell Crisis

The hallmark of sickle−cell anemia is the *sickle−cell crisis* (also sometimes known as a *vaso−occlusive crisis*), which is an episode of pain. They cannot be predicted and they vary widely among different individuals. In general 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. The pattern may occur as follows:

- The first day of the crisis is usually the worst, with pain in the arms, legs, and back. The pain is typically described as sharp, intense, and throbbing. Shortness of breath is common.
- Children often experience pain in the abdomen, which is probably caused by spasm or gas.
- Pain in the bones is common because blood obstruction can directly damage bone and because bone marrow is where red blood cells are manufactured.
- Sudden attacks of pain also frequently occur in the fingers or toes and in other bones and joints.
- 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.

Generally, people can resume a relatively normal life between crises. Some patients have few painful events; others may need to be hospitalized many times a year. Some patients can go months without a crisis and then have a cluster of severe attacks. Painful episodes sometimes become less frequent with increasing age.

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. 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. Effective pain medications are available to help reduce the severe pain of sickle−cell crises. Often, however, patients are not given the treatment they require:

- Many patients, their families, and even physicians are hesitant to use opioids aggressively because of fear of addiction. This fear, however, is nearly always unwarranted. Studies indicate that less than one in a thousand people who take long−term narcotics to alleviate chronic pain develop an addiction to the drug.
- In adults, 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.

Adult patients and parents of children with the disease should insist on aggressive pain−relief treatment. If physicians 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, although older patients with severe pain may also require intravenous administration.

- Some experts prefer morphine (Dilaudid) for frequent or prolonged episodes of pain. 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.
- 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 are proving to be very useful for sickle−cell patients.

Other side effects of opioids are vomiting and nausea, itching, and problems urinating. If the patient vomits or becomes nauseated, the physician 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, physicians 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, although when used as first−line therapy in an acute crisis, ketorolac is effective only in about half of episodes.
- Steroid hormone drugs are commonly used to treat pain caused by inflamed muscles and joints, and studies using these drugs along with opioids are reporting some success with sickle−cell patients. Such drugs include methylprednisolone (Medrol) and dexamethasone (Decadron, Hexadrol). 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.

Tramadol. Tramadol is a potent oral painkiller that 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.

Nitric Oxide and Arginine. Nitric oxide, a soluble gas, relaxes smooth muscles and dilates blood vessels. Evidence suggests that hemoglobin, which is released in large amounts by the abnormal sickle red blood cells, removes nitric oxide, which may be responsible for the blood vessels constriction and pain in sickle cell diseases. Nitric oxide is not the same substance as nitrous oxide, the so−called laughing gas used in dentistry.) Some studies indicate that inhaling nitric oxide may slow the disease process and improve symptoms. It is difficult to administer, however.

Arginine is a natural amino acid that is metabolized to nitric oxide, a chemical in the body that is important for relaxing blood vessels and which is often deficient in sickle cell patients. Important research suggests that this effect may be a cause of pain in sickle cell crises. Researchers are also investigating agents that convert to arginine. One early trial reported dramatic improvements in symptoms and risk for infection with the use of L−citrulline, a precursor to arginine. There were no significant side effects. More research is warranted.

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 agent 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 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.

Causes of Acute Chest Syndrome. The two primary causes of acute chest syndrome 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.
- Infarction. Infarction is blockage in the blood vessels that cuts off oxygen. Infarctions in acute chest syndrome may be caused by blood clots or fat embolisms that settle in the blood vessels in the lungs. (Fat embolisms are particles formed from fatty tissue in the bone marrow that enter and travel through the blood vessels.) Studies suggest that infarction is the cause of acute chest syndrome in about 16% of cases.

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 infectious agents, even agents 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.
- Use of bronchoscopy to identify infection. This is 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 (drugs that open the air passages). This treatment can be effective for some patients who are wheezing or have obstructed lung function.
- Antibiotics. Those used should 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 usually restricted to severe cases and are important if fat embolisms have developed. [*See Box Transfusion Therapy in Sickle Cell.*]

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 two 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.

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* (which can cause blood infections or meningitis).
- *Haemophilus influenza* (which is 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 agents in acute chest syndrome (*see below*).
- Gram−negative bacteria. This group of agents 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 physician. Adults with sickle cell should call the doctor if they have a have 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 six−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. Physicians should take a urine culture before beginning antibiotic treatment and another culture one to two weeks after treatment to be sure the infection has cleared up.

Using Antibiotics for Prevention. Antibiotics are the best approach for preventing 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. Unfortunately, many patients stop taking their antibiotics or the parents stop giving them to their children. Physicians are also concerned about developing bacterial resistance to common antibiotics and researchers warn that patients might experience break−through 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, and the following are important for everyone with sickle−cell disease:

- Vaccination against H*aemophilus influenza* (the major cause of childhood meningitis).
- Influenza vaccinations ("flu vaccines") every winter.
- Pneumococcal vaccine. All sickle−cell patients should be vaccinated with the pneumococcal vaccine. Protection lasts for over six years in most people. Children with sickle−cell disease should receive three doses of the pneumococcal conjugated vaccine (Prevnar) between two and six months of age, followed by two doses at age one, and then vaccinations at age two, five, and every 10 years afterward. (Some experts recommend every five years rather than every 10 years).
- Yearly tuberculosis test.
- Hepatitis B vaccine. (Anyone starting transfusion therapy should receive it if they had not been immunized as children.)

Stroke

After acute chest syndrome, stroke is the most common killer of patients with sickle−cell disease who are older than three years old. Between 8% and 10% of patients suffer strokes, typically at about age seven. 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. Sickle−cell patients are also at high risk for stokes 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.)

Transfusions for Prevention of Stroke. Compelling data show that regular (monthly) 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 five years of transfusions. Some centers are now administering transfusion therapy indefinitely. Complications from this treatment, however, can be considerable and more studies are needed to determine when transfusions can be safely stopped. In centers where transfusions are stopped after three years (which is still in the majority of centers), strokes occur in about of half of children. [*See Box* Transfusion Therapy in Sickle−Cell Disease.]

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. It is still not highly accurate, and many physicians are concerned about giving continual transfusions to every sickle−cell patient whose ultrasounds indicate risk.
- 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 physicians must make the best decisions they can.

Anticoagulation. Researchers have investigated anti−blood clotting agents, such as aspirin and heparin, for preventing stroke, but their use is controversial, and their effects on children are unclear and understudied. For example, one study on children with stroke from causes other than sickle cell report that this approach is safe but may not have offer any significant protection.

Anemia

Anemia is a significant characteristic in sickle−cell disease (which, in fact, 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 anemic 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.) [*See Box* Transfusion Therapy in Sickle−Cell Disease.]

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.

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% to 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.

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 might be beneficial in 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

Males, including children, with sickle−cell disease may also suffer from priapism, which is a prolonged and painful erection. 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. A surgical procedure that implants a shunt to redirect blood flow is sometimes performed. Inflatable penile implants may help maintain potency without causing priapism. One study suggests that treatment with the drug leuprolide can prevent repetitive and prolonged episodes of priapism in severely affected teenage boys with sickle−cell disease; further research is required, however.

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.

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 the have recurrent or severe pain from gallstones, the gallbladder may need to be removed. Minimally invasive procedures (using laparoscopy) that reduce possible complications are now available.

Damaged Spleen

The spleen of most adults with sickle−cell anemia is nonfunctional due to recurrent episodes of oxygen deprivation that eventually destroys it. A very serious anemic condition called *acute splenic sequestration* crisis (sudden spleen enlargement) can occur if the 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. [*See Box* Transfusion Therapy in Sickle−Cell Disease.]

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 can also cause bone loss, particularly the top of the thighbone, and pain in the hands and feet of children, which is known as the hand−foot syndrome. Pain due to oxygen loss in the bone marrow is common and may be responsible for persistent other nontypical symptoms. Ultrasound is a helpful tool in diagnosing and treating these abnormalities.

Leg Sores

Leg sores 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. The leg should be elevated and bed rest for a week or more is sometimes required for severe ulcers. Topical antibiotics, saline or zinc oxide dressings, or cocoa butter or oil are also used depending on severity. Skin grafts and transfusions have been helpful in some extreme cases.

Problems in Mental Functioning

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.

The Pregnant Woman with Sickle Cell

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

Patients who survive infancy are subject to other medical problems, including impaired physical development, gum disease, scarring of the retina, and leg sores.

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 also reduce the incidence of pain and acute chest syndrome. Regular transfusions, however, can have severe adverse effects however.

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 need 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).
- Before surgeries to reduce surgical complications. Some evidence suggests that a conservative transfusion regime is as effective as aggressive transfusions in these cases, but more research is needed.

Chronic Transfusions. Chronic transfusions are used in the following conditions:

- 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%.
- In patients with pulmonary hypertension and chronic lung disease.
- In patients with heart failure to improve quality of life.
- In patients with chronic kidney failure and severe anemia.
- In some patients who have unusually severe and protracted episodes of pain.

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. 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 for this purpose. Unfortunately, deferoxamine has some severe side effects and must be infused using a pump for 20 hours each day. Many patients then fail to continue with the treatment.

Oral forms of iron−chelation therapy (deferiprone, IC670) are currently in trials. Early studies on IC670 are promising, but more research is needed to determine any long−term adverse effects. Deferiprone is approved in Europe, but small studies suggest it is less effective than intravenous chelation therapy. It also has very serious complications and long−term effects, including liver scarring. Still one 2002 study reported that it was more effective than Desferal in removing iron stores in heart muscle tissue.

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.

WHAT ARE THE TREATMENTS AIMED AT SICKLE−CELL DISEASE ITSELF?

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.

Hydroxyurea and Stimulation of Fetal Hemoglobin (HbF)

Hemoglobin F (HbF, also called fetal hemoglobin) is a 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 hemoglobin F.

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 agent 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 sickled 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 the number of sickling crises, the number of transfusions, and life−threatening complications in this group, and the benefits appear to be long lasting. For example, a 2002 study reported that after four years patients who had taken the drug for at least two years experienced 30% fewer hospitalizations and 58% fewer transfusions than before they took hydroxyurea. Not all patients respond to hydroxyurea, and the best candidates for the treatment are not yet clear.

Studies on children are also proving to be very promising. It may be used for children with frequent pain episodes, a history of acute chest syndrome, and other severe complications. The response to hydroxyurea in children and teenagers

with sickle−cell disease is similar to the response in adults, and few severe adverse effects are being reported. A 2001 study suggested that the drug is effective and safe even in very small children (averaging 15 months). In the study, the drug was very well tolerated and may even have helped delay progression of disease in the spleen. Another study of children undergoing long−term hydroxyurea treatment indicated that hemoglobin F increase was sustained longer than in adults.

It is not a cure−all however; it has no effect on about 25% of patients, and it is still unknown whether it has any protective benefits over time. Parents should consult expert physicians. At this time, it should not be used during pregnancy.

Continued monitoring of hemoglobin F has been recommended by some experts who believe that the drug should be discontinued if there is no increase in hemoglobin F within six months. 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 leukemia, but long−term research is needed.

Decitabine. Decitabine is an agent usually used in cancer treatments that increases HbF. Small early studies are suggesting that it helps patients who have failed hydroxyurea and has only minor toxic side effects. More research is warranted.

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 agents 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 used to treat fungal skin infections) stops potassium from leaving and calcium from entering red blood cells, thereby preventing 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.

In addition, patients must be further qualified:

- They must be under age sixteen.
- They must have severe symptoms but no long term organ or neurologic damage.
- They must have genetically matched siblings who will donate their marrow.

Only about 7% meet the criteria for transplantation. 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.

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.

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

- 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.

Cord Blood. 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.

Gene Therapy

Some researchers are focusing on therapies that transfer certain genes to bone marrow that might prevent the sickling process. Gene therapy has successfully cured sickle cell disease in mice. It is not know if such techniques are applicable to humans, and even if they are, effective gene therapy would be years away.

WHAT ARE LIFE−STYLE MEASURES THAT CAN HELP MANAGE SICKLE−CELL DISEASE?

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).
- 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 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 agents 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.

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.

Warnings on Alternative and So−Called Natural Remedies

It should be strongly noted that alternative or natural remedies are not regulated and their quality is not publicly controlled. In addition, any substance that can affect the body's chemistry can, like any drug, produce side effects that may be harmful. Even if studies report positive benefits from herbal remedies, the compounds used in such studies are, in most cases, not what are being marketed to the public.

There have been a number of reported cases of serious and even lethal side effects from herbal products. In addition, some so−called natural remedies were found to contain standard prescription medication. Of specific concern are studies suggesting that up to 30% of herbal patent remedies imported from China having been laced with potent pharmaceuticals such as phenacetin and steroids. Most problems reported occur in herbal remedies imported from Asia, with one study reporting a significant percentage of such remedies containing toxic metals.

The following website is building a database of natural remedy brands that it tests and rates. Not all are available yet. http://www.ConsumerLab.com/

The Food and Drug Administration has a program called MEDWATCH for people to report adverse reactions to untested substances, such as herbal remedies and vitamins (call 800−332−1088).

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 physicians 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.
- *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. [*See* Where Else Can Help Be Found For Sickle−Cell Disease?]

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

WHERE ELSE CAN HELP BE FOUND FOR SICKLE−CELL DISEASE?

Sickle−Cell Disease Association of America, Inc. (http://sicklecelldisease.org). Call (800−421−8453) or (310−216−6363). The association has a hotline staffed by counselors and provides free educational materials and referrals to medical and support services in the patient's area.

The Sickle−Cell Disease Program, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, (http://www.nhlbi.nih.gov). Call (301−435−0055). The National Heart, Lung, and Blood Institute funds 10 comprehensive centers in the United States for sickle cell treatment and research.

A government site with excellent links (http://www.nlm.nih.gov/medlineplus/sicklecellanemia.html).

The Sickle Cell Information Center (http://www.emory.edu/PEDS/SICKLE). Call (404−616−3572). This is an excellent site with in−depth and very detailed information on sickle cell disease.

The Center for Sickle−Cell Disease (http://www.huhosp.org/sicklecell/default.htm). Call (202−806−7930).

Sickle Cell Advocates for Research and Empowerment, Inc. (http://defiers.com/index1.html). Call (718−884−9670).

The Sickle Cell Society (http://www.sicklecellsociety.org).

The Alliance of Genetic Support Groups (http://www.geneticalliance.org). Call (1−800−336−GENE) or (202−966−5557). This is a very helpful organization. It puts people in touch with support groups, genetic counselors, and provides information on some disorders.

National Organization for Rare Disorders (http://www.rarediseases.org). Call (203−746−6518) or (800−999−6673) or for hearing impaired (203−746−6927).

American Pain Society (http://www.ampainsoc.org). Call (847−375−4715).

American Society of Pediatric Hematology/Oncology (http://www.aspho.org). Call (847−375−4716).

Medic Alert (http://www.medicalert.org). Call (888) 633−4298. This organization provides bracelets or neck chain emblems with critical personal medical information and also keeps computerized medical records.

Find a Sickle−Cell Medical Center (http://www.rhofed.com/sickle/direct.htm).

National Collaborative Study of bone marrow transplantation (BMT) for sickle cell anemia (http://www.sickle.fhcrc.org).

Joint Center for Sickle Cell and Thalassemic Disorders (http://sickle.bwh.harvard.edu).

Site addresses health issues for African−Americans (http://blackhealthcare.com).

Blood and Marrow Transplant Information network (http://www.bmtnews.org).

Cord Blood Donor Foundation (http://www.cordblooddonor.org).

Review Date: 12/31/2002

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