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Sickle Cell Disease Information for Physicians and Other Health Care Professionals

Definition Sickling hemoglobinopathies are inherited disorders that result in production of an abnormal form of hemoglobin S, C or E, or a decreased synthesis of a beta globin chain. Sickle cell disease is a term for hemoglobin disorders characterized by the predominant production of hemoglobin S.

Clinical Symptoms Any sign of illness in an infant with sickling disease is a potential medical emergency. Acute and chronic tissue injury can occur when sickled cells cause vascular occlusion. Sickling diseases can cause severe pain anywhere in the body, but most often in the hands, arms, chest, legs and feet. Complications may include, but are not limited to, the following:

- **Sepsis** – The first sign of infection may be a fever of 101⁰ F or greater. These children require immediate medical attention. Children with sickle cell diseases are very susceptible to pneumococcal infections.
- **Acute chest syndrome** – A serious condition caused by infection and/or trapped sickled red blood cells in the lungs. Symptoms may include dyspnea, coughing and chest pain.
- **Hand-and-foot syndrome** – This painful swelling of the hands and feet is due to severe vascular occlusion.
- **Splenic sequestration crisis** – Early signs include pallor, enlarged spleen and pain in the abdomen due to accumulation of sickled cells within the spleen. This complication can result in circulatory collapse and shock, with sudden death, if not recognized and treated immediately.
- **Aplastic crisis** – The bone marrow temporarily stops producing red blood cells, resulting in severe anemia. The child may appear pale, tired, and less active than usual.
- **Stroke** – Cerebral vascular occlusion due to sickled cells can affect even very young children. Any loss of consciousness or weakness in an extremity should be evaluated promptly.
- **Painful episodes** – The pain of sickling disorders is acute and can be quite severe; even very young children may require prescription medications for pain relief.

Newborn Screening and Definitive Diagnosis In Illinois, newborn screening for sickle cell disease is performed by high performance liquid chromatography (HPLC) testing to determine the presence of abnormal hemoglobins (Hgb) in whole blood. Unaffected infants will have mostly fetal hemoglobin (Hgb F) and some adult hemoglobin (Hgb A). HPLC has been shown effective in detecting hemoglobinopathies characterized by synthesis of an abnormal hemoglobin molecule immediately after birth. A baby testing positive for a form of sickle cell disease will have Hgb F with Hgb S and possibly another abnormal hemoglobin such as Hgb C, Hgb E or beta thalassemia. **All abnormal newborn screening test results indicating a sickle cell disorder require appropriate confirmatory blood tests, sometimes including testing of parents and siblings for actual diagnosis. Referral to a pediatric hematologist for evaluation and diagnostic testing is recommended within the first month of life and should not be delayed until the infant is older.** If newborn screening results indicate a less serious hemoglobin disorder or carrier status, referral to a pediatric hematologist for parental education and counseling is recommended. **Even small transfusions may cause false negative screening test results and any results indicating that the baby was transfused require repeat testing 90 days after the last transfusion.**

There are several recommended testing methods for diagnosis of sickling disorders and other hemoglobinopathies:

Hemoglobin electrophoresis including both cellulose acetate and citrate agars (one is not sufficient), isoelectric focusing and high performance liquid chromatography are considered proven, reliable and accurate methods for defining an infant's hemoglobin phenotype. All siblings of infants diagnosed with a sickle cell disease should be tested; genetic counseling services should be offered to parents.

Treatment The National Institutes of Health clinical guidelines for management of sickle cell diseases state, **“Penicillin prophylaxis should begin by 2 months of age for infants with suspected sickle cell anemia, whether or not the definitive diagnosis has been established.”** Antibiotic therapy should continue until at least 5 years of age. Normal dosage for an infant is 125 mg of penicillin twice a day until 3 years of age, when dosage is increased to 250 mg twice a day. An alternative antibiotic is available for children who are allergic to penicillin therapy. Prescription pain medication also may be indicated during sickling crises. Health care monitoring and maintenance with appropriate immunizations is imperative to the health of the baby, and pneumococcal conjugate vaccine immunizations also are recommended, beginning at 2 months of age.

Incidence Sickle cell diseases affect more than 50,000 Americans, primarily those of African heritage, but also those of Mediterranean, Caribbean, South and Central American, Arabian or East Indian heritage. About one out of every 375 African-American children is affected by sickle cell disease, making it one of the most prevalent genetic diseases in the United States. Illinois started universal newborn screening for sickle cell diseases in 1989; each year approximately 100 infants are diagnosed with a form of sickle cell disease.

Inheritance Patterns Sickle cell diseases are inherited in an autosomal recessive pattern. As an autosomal recessive disorder, the parents of a child with a sickle cell disease are usually unaffected, healthy carriers of the condition and have one normal gene and one abnormal gene. With each pregnancy, carrier parents have a 25 percent chance of having a child with two copies of the abnormal gene, resulting in a hemoglobinopathy. Carrier parents have a 50 percent chance of having a child who is an unaffected carrier and a 25 percent chance of having an unaffected, non-carrier child. These risks hold true for each pregnancy.

SS sickle cell disease occurs when one gene for production of Hgb S is inherited from each parent. Other sickling disorders occur when the child inherits a gene for Hgb S from one parent and a gene for another abnormal form of hemoglobin (C, E or beta thalassemia) from the other parent. SS disease is the most common and the most serious type of sickle cell disease. Other forms include SC disease and sickle beta thalassemia. The severity of sickling disorders varies among affected individuals.

Genetic counseling services are recommended for individuals with sickle cell diseases and for those who carry the abnormal hemoglobins, particularly concerning future pregnancies. These individuals may have questions about the disorders that are best answered by hematology specialists and genetic counselors.

Physiology Normal blood contains mostly hemoglobin A. Fetal hemoglobin (Hgb F) is found in newborns, normally through the third month of life. With the presence of abnormal hemoglobin (Hgb S), red blood cells change from their usual biconcave disc shape to a sickle shape during de-oxygenation. Upon re-oxygenation, the red blood cell initially resumes its normal shape but, after repeated cycles of “sickling and unsickling,” the red blood cell is permanently damaged and hemolyzes. This hemolysis results in anemia, which is a hallmark of sickling diseases. Sickled cells also restrict vascular blood flow and can result in the clinical manifestations of the disease.

Key Points for Parents Avoid overly alarming the child’s parents if the diagnosis has not yet been confirmed. If the child needs additional testing or diagnostic evaluation, make certain the parents understand the importance of following the pediatrician’s and/or specialist’s recommendations for additional testing and referrals.

Follow-up After Confirmation of Diagnosis These guidelines should be followed after a diagnosis of sickle cell disease has been confirmed:

1. Regular visits to a comprehensive sickle cell program or a pediatric hematologist and strict compliance in antibiotic administration are crucial to the health and future well-being of the baby. Parents should understand the importance of twice-daily doses of prophylactic penicillin as an effective measure to reduce both morbidity and mortality from pneumococcal infections in infants with all forms of sickle cell diseases.
2. Parents of infants with sickle cell disease should be instructed in all aspects of routine child care. They should be able to accurately check the infant’s temperature. They must be able to recognize early symptoms of complications, including the warning signs of inactivity, fever, pallor and respiratory distress. Parents should be taught to palpate the infant’s spleen and to recognize splenic enlargement. Parents must understand the importance of prompt assessment of the infant by a pediatric hematologist when fever, pallor, unexplained irritability, diarrhea, vomiting or other signs of illness are present. Fever of 101⁰ F or greater requires immediate medical evaluation.
3. Provide a list of support services available in the community, such as the local health department and Early Intervention services. **The Sickle Cell Disease Association of Illinois offers family support and educational services to the families of children and adults with sickle cell diseases. The Association may be contacted at 773-526-5016.**
4. Additional information about newborn screening can be found at:
 - Baby’s First Test: <http://www.babysfirsttest.org/>
Health Resource and Service Administration (HRSA), Grant no. U36MC16509, Quality Assessment of the Newborn Screening System.
 - National Center for Biotechnology Information: <http://www.ncbi.nlm.nih.gov/gtr/>
National Center for Biotechnology Information, U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda MD, 20894 USA.