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## **Beta Thalassemia Disease (Cooley's Anemia) Information for Physicians and Other Health Care Professionals**

**Definition** Beta thalassemia is an inherited red blood cell disorder that results in the complete absence or decreased synthesis of the beta globin chains of hemoglobin. Individuals with beta thalassemia trait or beta thalassemia minor are heterozygous for beta thalassemia, or simply a carrier of beta thalassemia. Individuals with beta thalassemia major are homozygous for beta thalassemia, thus have two copies of defective beta-globin genes, and develop disease. The complete absence of beta-globin synthesis is denoted as  $\beta^0$  thalassemia and the reduced synthesis is denoted as  $\beta^+$  thalassemia. Unlike hemoglobinopathies, which cause disease through structural defects of hemoglobin, thalassemias cause disease due to an affect on the production of hemoglobin. The decrease in beta-globin leads to a relative excess of alpha-globin chains, causing disease.

**Clinical Symptoms** Infants with beta thalassemia develop severe anemia within the first few months of life and must be treated with regular blood transfusions. Without transfusion and proper treatment, beta thalassemia disease causes death within the first two years of life. Additional complications include infection, bone deformities, progressive hepatosplenomegaly and severe iron overload requiring chelation therapy. There is a wide range of clinical severity, especially between individuals with  $\beta^0$  thalassemia and  $\beta^+$  thalassemia. However, individuals with  $\beta^0$  thalassemia will require and be dependent on lifelong blood transfusions.

Carriers of beta thalassemia do not have disease and will not develop disease over time. Some carriers may experience mild anemia, which may be inaccurately diagnosed as iron deficiency anemia, but do not require a special diet or medical treatment.

**Newborn Screening and Definitive Diagnosis** In Illinois, newborn screening for beta thalassemia disease is performed by high performance liquid chromatography (HPLC) testing to determine the presence or absence of 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 beta thalassemia will have higher than normal fetal hemoglobin (Hgb F) and reduced levels or no adult hemoglobin (Hgb A). **All abnormal newborn screening test results indicating beta thalassemia 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 hemoglobinopathies and thalassemias: **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 hemoglobinopathy or thalassemia should be tested; genetic counseling services should be offered to parents.

**Treatment** The basic treatment for beta thalassemia is regular blood transfusions, typically administered every four weeks. Children who are transfused appropriately grow well and have a normal life. However, to live past their 20's, those with beta thalassemia major also may need chelation therapy to remove excess iron released from the hemoglobin of transfused cells that continuously break down. If iron chelation is not performed for those with beta thalassemia major, iron may build up in the body ultimately damaging vital organs such as the heart, liver and endocrine glands. Cure of the disease only can be achieved by bone marrow transplant, which relies on a fully matched sibling. However, roughly 20 percent of patients will have a fully matched donor.

**Incidence** Beta thalassemia is a fairly common blood disorder worldwide, affecting an estimated 100,000 infants worldwide each year. It is estimated that approximately one out of 25,000 infants in the United States are born with thalassemia each year; this number increases to one in 100,000 infants born each year worldwide with thalassemia. There are an estimated 1,000

people living with beta thalassemia in the United States and an unknown number of beta thalassemia carriers. The disease occurs most frequently in those of Mediterranean, Asian or African heritage or ancestry.

**Inheritance Patterns** Beta thalassemia is inherited in an autosomal recessive pattern. Beta thalassemia disease occurs when one affected gene for production of beta-globin is inherited from each parent. The genes for beta-globin chain production are located on chromosome 11. There is one beta-globin gene on each chromosome 11, for a total of two. In beta thalassemia carriers, one beta-globin chain is abnormal. In beta thalassemia disease, two beta-globin chain genes are abnormal.

As an autosomal recessive disorder, the parents of a child with beta thalassemia disease are usually unaffected, healthy carriers of the condition and have one normal beta-globin gene and one abnormal beta-globin gene. Beta thalassemia carriers have a 50/50 chance to pass on the abnormal gene to their children. A child of two carriers has a 25 percent chance of receiving two abnormal genes and developing the disease, and a 50 percent chance of being an unaffected carrier of the abnormal gene. There is also a 25 percent chance a child would receive two normal genes and therefore be unaffected. These risks hold true for each pregnancy between two beta-thalassemia carrier parents.

**Genetic counseling services are recommended for individuals with beta thalassemia and for those who carry the abnormal beta-globin gene, 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. Hemoglobin A is comprised of equal quantities of alpha-globin chains and beta-globin chains of hemoglobin. Hemoglobin A requires these globin chains in equal proportions to function and transport oxygen properly. The beta thalassemia defect leads to reduced or no production of beta-globin chains, which in turn leads to an excess of alpha-globin chains. These excess alpha-globin chains prevent the development of normal red blood cells, leading to an insufficient production of both the quantity and quality of red blood cells. As a result, the body does not receive enough oxygen because the red blood cells cannot transport it, resulting in the clinical manifestations of the disease. The disease typically presents after the disappearance of fetal hemoglobin (Hgb F), found in newborns and present through the third month of life. The two major consequences of the disease are severe anemia and expansion of the bone marrow in an attempt to produce more and more red cells to fight anemia. These consequences lead to poor growth, impaired physical activity, bone deformities, fragile bones and enlargement of the liver and spleen.

**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 beta thalassemia disease has been confirmed:

1. Regular visits to a comprehensive thalassemia center or a pediatric hematologist are crucial to the health and future well being of the baby.
2. Regular transfusion therapies with safe and appropriately processed blood, combined with regular and effective iron chelation greatly increase patients' survival and quality of life.
3. Provide a list of support services available in the community, such as the local health department and early intervention services.
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.