



**NEWBORN SCREENING  
OFFICE OF HEALTH PROMOTION**

535 W. Jefferson St., 2<sup>nd</sup> Floor  
Springfield, IL 62761  
Phone: 217-785-8101  
Fax: 217-557-5396

## **Urea Cycle Disorders Information for Physicians and Other Health Care Professionals**

**Definition** Urea cycle disorders are a group of inherited conditions of amino acid metabolism, each caused by a specific deficiency of one of the normally expressed enzymes of the urea cycle.

**Newborn screening in Illinois includes testing for the following urea cycle disorders:**

- Citrullinemia – argininosuccinate synthetase deficiency
- Argininosuccinic acidemia – argininosuccinate lyase deficiency
- Argininemia – arginase deficiency

**Note:** Other urea cycle disorders may not be detected by newborn screening.

**Clinical Symptoms** Symptoms of citrullinemia and argininosuccinic acidemia present in the newborn period. These infants appear normal at birth with onset of clinical symptoms beginning at 1 to 3 days of age. Clinical features are the result of the development of hyperammonemic encephalopathy and include poor feeding, lethargy leading to coma, hyperventilation, muscle tone abnormalities and, in the late stages, seizures and ultimately death. Vomiting may occur and hepatomegaly is occasionally observed. Argininemia may present with paraplegia, tetraplegia and ataxia.

**Newborn Screening and Definitive Diagnosis** In Illinois, newborn screening for urea cycle defects is performed using tandem mass spectrometry. False positive and false negative results are possible with this screening. **Infants with a presumptive positive screening test require prompt follow-up and, when notified of these results, the clinician should immediately check on the clinical status of the baby and refer the infant to a metabolic disease specialist.**

**Treatment** Early diagnosis and treatment is essential for an improved prognosis. If left untreated, infants with these conditions will suffer progressive neurological deficit and death. Treatment for argininosuccinic acidemia and citrullinemia is dietary, and includes a special medical formula with arginine supplements and high caloric intake as well as medications to control problems of hyperammonemia. Liver transplantation is an effective treatment. **Urea cycle disorders may result in severe hyperammonemia, and infants with these disorders require prompt treatment, which may include hemodialysis.**

**Incidence** Argininosuccinic acidemia has an estimated incidence of approximately one in 70,000 births. The incidence of citrullinemia is estimated to be approximately one in 100,000 births.

**Inheritance Pattern** These disorders are inherited in an autosomal recessive pattern. As an autosomal recessive disorder, the parents of a child with one of these conditions are 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 and the resulting urea cycle defect. 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 would hold true for each pregnancy. All siblings of infants diagnosed with a urea cycle disorder should be tested; genetic counseling services should be offered to the family.

**Physiology** The urea cycle is a metabolic pathway that converts ammonia and bicarbonate to urea, for the purpose of removing waste nitrogen from the body. Enzyme defects due to inborn errors of metabolism in the urea cycle lead to high levels of ammonia. Elevated ammonia in blood and tissues is neurotoxic, leading to the clinical findings of these disorders.

**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 that 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 a urea cycle defect has been confirmed:

1. Parents should understand that treatment is lifelong and that compliance with dietary management is imperative to the child's health, growth and development.
2. Infants and children with a urea cycle defect should have regular follow-up appointments with a metabolic disease specialist.
3. **Parents should be warned that if infant shows symptoms, such as vomiting or lethargy, they should seek immediate medical attention.**
4. Long-term management, monitoring of ammonia levels and compliance with treatment recommendations are essential to the child's well-being. A multi-disciplinary approach including the following specialities is recommended: pediatrics, genetics and nutrition. Parents should understand that treatment is not curative; and that all morbidity cannot necessarily be prevented.
5. Genetic counseling services are recommended. A list of genetic counselors and geneticists whose services are available through the Illinois Department of Public Health should be given to the parents if they have not already seen a geneticist.
6. Provide a list of available support services in the community, such as the local health department, Early Intervention service providers and the University of Illinois at Chicago Division of Specialized Care for Children (DSCC).
7. 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.