



Maple Syrup Urine Disease (MSUD) Information for Healthcare Professionals

Maple Syrup Urine Disease (MSUD) is an inherited metabolic condition in which the branched-chain amino acids (leucine, isoleucine and valine) are ineffectively catabolized. The branched-chain alpha-ketoacid dehydrogenase (BCKD) complex in the mitochondrial membrane is responsible for breakdown of these three amino acids. A deficiency in one of the six enzymes forming the complex leads to high levels of leucine, isoleucine and valine in the plasma, cerumen, and urine. **Untreated, MSUD usually leads quickly to encephalopathy, spasticity, coma, seizures and death.**

✓ Clinical Symptoms

Babies with classic MSUD usually appear normal at birth. Within the first few days of life, feeding difficulties, irritability and vomiting become apparent. This is often followed by failure to thrive and progressive neurological deterioration, characterized by lethargy, tachypnea, coma and seizures. A high-pitched cry is common, as is muscular rigidity, or alternating periods of hypo- and hypertonicity. There are three other forms of MSUD: intermediate, intermittent and thiamine-responsive. These alternate forms represent partial activity of the BCKA complex, and are generally less severe and of later onset than the classic neonatal form. **The intermittent form is not usually detected by newborn screening.**

✓ Incidence

MSUD occurs in less than 1 in 100,000 births. Some Amish and Mennonite populations in the United States, due to a founder mutation, may have an incidence as high as approximately 1 in 300. It is also more common in people of French-Canadian ancestry.

✓ Genetics of MSUD

Mutations are known in four genes that encode proteins of the branched-chain alpha-ketoacid dehydrogenase (BCKA) complex. The most common mutations are found in *BCKDHA*, the gene for the E1 α subunit of the BCKA complex. These mutations are most often associated with the classic (neonatal-onset) form of MSUD.

✓ Inheritance

MSUD is inherited in an autosomal recessive pattern. Parents of a child diagnosed with MSUD are unaffected. These individuals are carriers of the condition and have one normal copy of the gene coding for the BCKA complex and one abnormal copy. Each pregnancy between carrier parents has a 25% chance of producing a child affected with MSUD, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ Treatment

Emergency treatment consists of hemodialysis and/or administration of a specialized nutritional solution in order to quickly reduce serum levels of the branched-chain amino acids. Ongoing management involves dietary protein restriction of the branched-chain amino acids, supplementation with medical formula, and frequent monitoring of blood concentrations of branched-chain amino acids. Avoidance of fasting and a management plan for infection are important in preventing catabolic crisis. Prognosis is better the earlier treatment is begun. In the classic form of MSUD, prognosis is best when treatment is initiated before 14 days of life. Liver transplantation has been reported to successfully reverse symptoms.

✓ **Screening Methodology**

Newborn screening for MSUD 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***. False positives are possible and may occur if the specimen is drawn from pre-term infants, submission is delayed, or if the specimen has been exposed to heat. False negatives can result if an infant has had a blood transfusion. The newborn screen should be performed 90 days post-transfusion.

✓ **What to do After Receiving Presumptive Positive MSUD Screening Result**

- 1) **Consult with pediatric metabolic specialist.**
- 2) **Evaluate the newborn. Individuals should be evaluated for clinical symptoms including lethargy, feeding problems, vomiting, and tachypnea. If infant is symptomatic, initiate emergency treatment to reduce serum branched-chain amino acids.**
- 3) **Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.**
- 4) **Call KS Newborn Screening Program at 785-291-3363 with questions about results.**
- 5) **Report Clinical Findings to Newborn Screening Program at 785-291-3363.**

✓ **Confirmation of Diagnosis**

A positive newborn screening result requires immediate evaluation for symptoms of MSUD.

Diagnostic testing, including plasma amino acids and urine organic acids, should be undertaken in consultation with a metabolic disease specialist, to confirm the diagnosis. Patients should be followed at regular intervals by a metabolic specialist and a metabolic nutritionist.

✓ **Communication of Results to Parents**

If a newborn has a presumptive positive MSUD newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with MSUD, the following points should be conveyed to parents:

- ***Treatment is life-long. While effective, it does not prevent all medical problems.***
- ***Compliance with treatment is necessary for the best outcome.***
- ***Parents who have a child with MSUD have a 25% chance with each pregnancy of having another affected child.***
- ***Prenatal testing for pregnancies at 25% risk is available when both parents are confirmed carriers.***

For consultation, contact:

Bryce Heese, MD
Biochemical Genetics
Children's Mercy Hospital- Kansas City, MO

Clinic phone: 816-234-3771
Hospital Operator: 816-234-3000
Office Fax: 816-302-9963