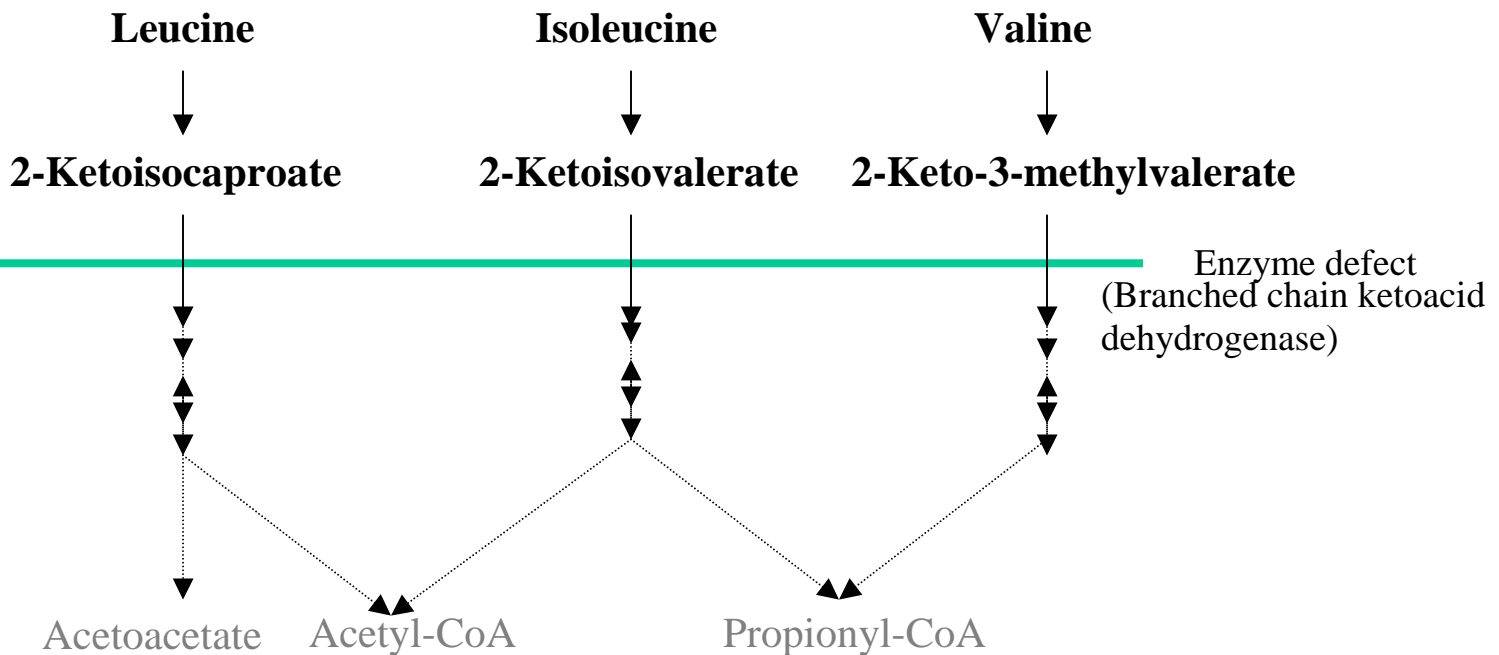


ACUTE ILLNESS PROTOCOL
ORGANIC ACIDEMIAS
MAPLE SYRUP URINE DISEASE (MSUD)

Maple syrup urine disease (MSUD) is an organic acid disorder* but is often classified as an amino acid disorder because of increased levels of branched chain amino acids as well as the organic acids. The central emergency features of MSUD are profound metabolic ketoacidosis and brain edema with lethargy progressing to coma.

**Organic acids are distinguished from amino acids in that they do not contain nitrogen.*

PATHOPHYSIOLOGY



Patients with MSUD are unable to metabolize the branched chain ketoacids. As a consequence, they have increased ketoacids and the precursor branched chain amino acids (leucine, isoleucine and valine). The toxic metabolic components are **leucine** and the **ketoacids**. When excessive protein is ingested or, more frequently, when the

infant/child is under metabolic stress from an acute illness (febrile upper respiratory infection, gastroenteritis, etc.) or in the immediate neonatal period, the increased metabolic rate requires many more calories than the child is ingesting, the cells begin to break down protein to supply the needed calories (catabolism). In MSUD, this results in marked increases in the branched chain amino acids and corresponding ketoacids, resulting in metabolic ketoacidosis and leucine toxicity. The leucine further increases because its high level (and the high levels of isoleucine and valine) block transport of other amino acids into the cells, thus depleting cells of amino acids required for incorporation of leucine back into protein. Brain edema is probably a result of high levels of osmotically active amino acids entrapped in brain cells by the high leucine levels producing increased intracellular osmolarity plus low extracellular sodium levels, both acting together to cause movement of water into the cells.

PRESENTATION

Well at birth but, symptoms may develop quite rapidly within 4 -7 days. Later in childhood similar symptoms develop during acute illness.

- poor suck, disinterest in feeding
- lethargy
- weight loss
- neurological deterioration with alternating hypertonia and hypotonia
- dystonic “decerebrate-like” extension of the arms
- seizures
- coma
- pseudotumor cerebri and/or bulging fontanelles occasionally seen
- maple syrup/burnt sugar like odor (from urine, bodily secretions & ear wax)

Presentation varies depending on the severity of the metabolic defect. The neonatal form presents in the first week of life with a life-threatening illness. Survivors of severe neonatal episodes are often neurologically devastated, when treatment was delayed. The infantile or late-onset form has a more insidious presentation with failure to thrive, developmental delay, and perhaps other neurologic features. Intermittent forms of MSD are also described. All forms can have acute severe life-threatening decompensatory episodes.

Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children. Listen to them !!!

ASSESSMENT

- vital signs, cardiovascular stability
- hydration status

- presence of fever; signs of infection
- neurologic status; evidence of increased intracranial pressure

LABS

Blood

- **plasma amino acids**
- **newborn screening** (via tandem mass spectrometry or 'Guthrie testing' – call lab if suspect)
- (arterial) blood gas
- electrolytes, glucose
- CBC, differential WBC count, platelets
- Serum amylase, lipase (pancreatitis can accompany metabolic episodes)
- ammonia (in ice STAT to lab) if diagnosis not certain
- lactate if diagnosis not certain

Urine

- **organic acids**
- **urinalysis for ketones**
- **DNPH test**

- as needed, cultures of blood, urine and throat

Warning: avoid lumbar puncture unless absolutely necessary – brain edema may be present and LP could cause herniation

Neonatal MSUD may not display marked abnormalities on routine tests and may not have metabolic acidosis. If hyperammonemia is present it is usually mild ($<130 \mu\text{mol/L}$). CBC and blood lactate are usually normal. The **MAIN** abnormalities found are in plasma aminoacids and urine organic acids. The DNPH test (2,4 dinitrophenylhydrazine) detects elevated 2-oxoacids in the urine and is a useful rapid screening test.

IMMEDIATE TREATMENT

1. **Discontinue** natural protein.
2. Provide the **large amount of calories** needed (120-140 kcal/kg/day).
3. Provide **fluids and sodium** to treat dehydration, reestablish normal perfusion and urine output, and **avoid hyponatremia**.
4. **Enteral therapy** with special formula that contains all required amino acids but is free of the branched chain amino acids
5. **Identify and treat** the infection or other causes of the metabolic stress.

SPECIFICS OF TREATMENT

1. **IV fluid therapy**
D10/normal saline with 20 meq KCL at 1 ½ times maintenance for 1-2 hours.

2. Stat laboratory tests

As described above

3. Branched chain amino acid-free formula

This medical product special formula can be made up by the pharmacy. The pharmacy must be supplied with the exact recipe.

An example is Ketonex 2 (Ross). This medical product formula provides 30 grams of protein equivalents and 410 calories per 100 grams of powder. It should be made up as a 20-25 kcal/oz solution. For an infant, the Ketonex 2 should provide 3-4 grams protein/kg/day. For a child, it should provide 2-3 grams protein/kg/day.

Ex: For 14 kg child, 120 grams Ketonex 2 powder in water to 22 oz. provides 2.6 grams protein/kg and 35 kcal/kg.

There are a number of other medical product formulas (see below) The only major differences are the amount of protein equivalents and calories per 100 grams of powder. For instance, Ketonex-1 has only 15 grams protein equivalents but 480 calories per 100 grams powder. Certain of these medical product formulas is appropriate only for infants and others for both children and adults. The table below lists the pertinent information about each of the products.

<u>Product</u>	<u>Supplier</u>	<u>Designation</u>	<u>Nutrition</u>	
			<u>Prot Eq (g)</u>	<u>Energy (kCal)</u>
Ketonex 1	Ross	Infant	15	480
MSUD 1	Milupa*	Infant	41	280
MSUD Analog	SHS	Infant	13	475
Ketonex 2	Ross	Child/Adult	30	410
BCAD-2	Mead Johnson	Child/Adult	24	410
MSUD 2	Milupa*	Child/Adult	54	300
MSUD Maxamaid	SHS	Child	25	309
MSUD Maxamum	SHS	Adult	39	297
Complex MSUD Drink Mix	Applied Nutrition	Child/Adult	25	410
Complex MSUD Amino Acid Blood	Applied Nutrition	Child/Adult	77	323
Complex MSUD Amino Acid Blood	Applied Nutrition	Child/Adult	21	575

*Distributed in the U.S. by Mead Johnson

L-alanine and L-glutamine, each at 250 mg/kg/day, should be added to the medical product. Both of these amino acids are reduced during acute ketoacidotic episodes of MSUD.

If one of the special formulas is unavailable, **BUT ONLY IF ONE OF THEM IS UNAVAILABLE**, pedialyte orally or Pro-Phree in water can be given to provide calories as a **temporary** measure until the child can be transferred to a metabolic center or the special medical product formula obtained. The standard recipe for Pro-Phree is to add 125 grams Pro-Phree to water for total volume of 960 ml, providing a 20 kcal/oz solution. If the infant/child does not feed, pass NG or J tube for feeding. If enteral feeding is not tolerated, can provide the amino acids IV with the special MSD-TPN amino acid mixture available through PharmaThera in Memphis, TN (Tel: 800-767-6714). It will be supplied within 24-48 hours as a 5 liter solution. The MSD-TPN is added to the IV fluids to supply 1.5-2.0 grams protein/100 ml.

4. **Calories**

Achieve a **caloric intake** of 120-140 kcal/kg/day with combination of enteral formula and IV glucose and Intralipid. Approximately 40-50% of the calories should be as Intralipid and formula.

5. **Evaluate the lab results, intake and clinical status.** Aims are:

- a. Provide **120-140 kcal/kg/day** and sufficient protein as amino acids free of the branched chain amino acids
- b. Eliminate **ketoacidosis** as determined by
 - serum bicarbonate level of 24 meq/L
 - absence of ketones in urine
 - negative urine DNPH test
- c. Maintain **serum sodium** at 140-145 meq/L. Monitor urine sodium output to establish loss and replacement requirement
- d. Measure **plasma amino acids** q12h. Levels should be reduced to:
 - leucine < 300 umol/L
 - isoleucine 300 umol/L
 - valine 400 umol/L

It is important to realize that isoleucine and valine levels may drop rapidly and that very low levels (isoleucine < 100 umol/L and valine < 200 umol/L) will keep the leucine level from dropping by limiting protein synthesis. Low levels will also allow more leucine to enter brain by providing less transport competition and thus will produce or enhance brain edema and neurological complications. Add isoleucine and valine at 100-150 mg/kg/day to maintain these levels.

- e. Less irritability, increased alertness, no vomiting, reduced hyperreflexia

6. As **serum sodium** approaches 140-145 meq/L, reduce IV fluids to D10/.45 normal saline and monitor serum sodium closely (hyponatremia enhances brain edema in MSUD). After 24 hours, adjust sodium intake to provide 4 meq/kg/day. Too much sodium will complicate fluid management.

7. If **serum bicarbonate** is below 14 meq/L and blood pH < 7.2, give IV bolus NaHCO₃ as 2.5 meq/kg over 30 minutes, then 2.5 meq/kg/day until serum bicarbonate is 24-28 meq/L.

8. If **blood glucose** rises > 200 mg/dL after one hour of IV infusion, begin insulin infusion at 0.05-0.1 unit/kg/hr until blood glucose is controlled.
9. If neurological signs worsen (vomiting, lethargy, hyperreflexia, clonus), suspect severe **cerebral edema**. Critical edema most often occurs during IV therapy, either due to serum sodium below 135 meq/L or continued ketosis and vomiting. Brain edema with brain stem herniation is the most frequent cause of death in MSUD. If suspected, obtain brain CT or MRI. If severe edema confirmed, infuse mannitol at 1- 2 grams/kg over 30-40 minutes. Add lasix for diuresis but carefully monitor serum sodium to maintain concentration in the 140-145 meq/L range. Can infuse hypertonic saline to maintain the level.
10. **Vomiting** is the nemesis of MSUD. It provokes a ketoacidotic episode and complicates enteral therapy. Zofran at 2-4 mg every 6-8 hours can be effective in controlling vomiting.
11. **Hemodialysis** should be a last resort but may be lifesaving in a neonate who presents with coma and seizures and in whom IV therapy may not correct the profound metabolic derangements in time to prevent death from cerebral edema with brain stem compression. This could also be true for an older infant or child (or even adult). The Renal Service should be alerted as soon as hemodialysis is considered, well before the decision to hemodialyze is made, so that adequate preparations can be made in advance.

RECOVERY

Once the patient is stable and accepting enteral feeding, the plasma amino acids must **be monitored daily** to reestablish amino acid homeostasis. On the basis of these levels, the branched chain amino acid-free medical formula with added source of branched chain amino acids and the low protein foods are adjusted to aim for plasma levels as follows:

leucine 175 umol/L
isoleucine 200 umol/L
valine 300 umol/L
Other amino acids WNL

This will require careful attention to the amount of medical formula ingested, the amount of protein added to the formula, the amount of low protein foods ingested and the amount of supplemental isoleucine and valine added to the formula (each supplement should be available in the pharmacy as a 100 mg/10 ml solution)

In conjunction with this protocol, please call or have paged the genetics metabolism fellow on call, or failing this, the metabolic attending on call at your hospital or nearest pediatric tertiary care center