

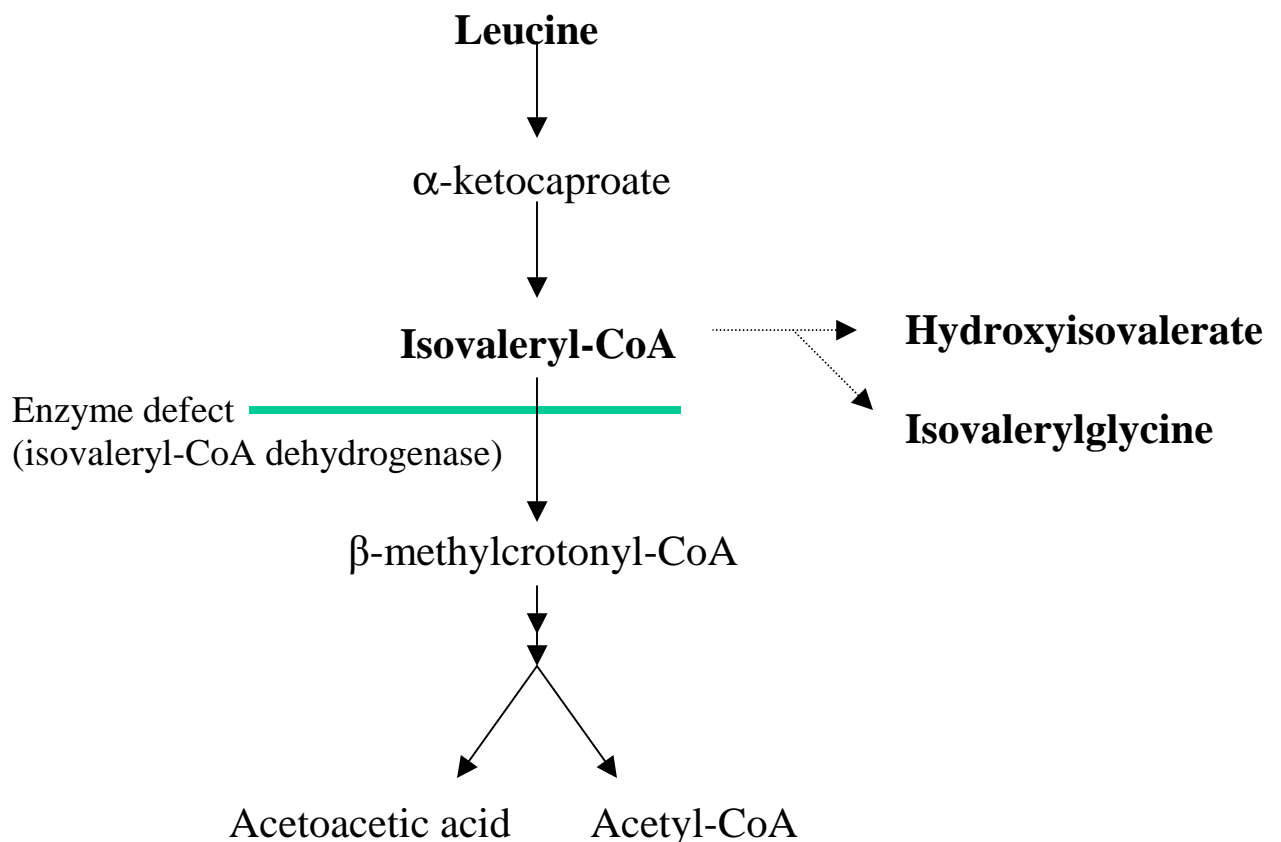
## ACUTE ILLNESS PROTOCOL ORGANIC ACID DISORDERS

### ISOVALERIC ACIDEMIA

The organic acidemias comprise a group of metabolic disorders in which the defect produces an accumulation of organic acids\*. The central emergency features of the organic acid disorders are profound metabolic **ketoacidosis** and **hypoglycemia**. The inheritance of Isovaleric acidemia is autosomal recessive. It is often referred to as the “sweaty foot syndrome” due to the characteristic odor of body and body fluids produced by it.

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

### PATHOPHYSIOLOGY



Catabolic stress such as normal perinatal catabolism or febrile illness (e.g. infection) produces endogenous proteolysis. The released amino acids add to the amino acid pools and are degraded within the relevant pathways, producing increased amounts of the organic acid intermediates. When excessive protein is ingested, a similar increase in available amino acids occurs. When there is a metabolic defect after the amino acid has lost its nitrogen in the course of degradation (see the pathway above), the esterified organic acid-CoA accumulates. Much of the esterified organic acid is converted to the parent organic acid and other organic acid metabolites.

The increased metabolite measured in urine and/or blood in these disorders is the organic acid per se and, in urine, the related metabolites. The increased organic acids overwhelm the body's acid-base balance, resulting in metabolic acidosis. This metabolic stress produces an increased need for cellular energy, which is provided by enhanced degradation of glucose, resulting in hypoglycemia. The hypoglycemia is exacerbated by inhibition of gluconeogenesis induced by one or more of the accumulated organic acids. The hypoglycemia sets in motion hormonal changes that cause release of free fatty acids from adipose tissue. The fatty acids are transported into mitochondria as carnitine conjugates where they are  $\beta$ -oxidized to ketones, producing ketosis. The increased organic acid also inhibits the urea cycle producing hyperammonemia, glycine degradation producing hyperglycinemia, and hematopoiesis resulting in neutropenia. Hence, the constellation of laboratory findings in these organic acid disorders:

**Ketoacidosis**  
**Hypoglycemia**  
**Neutropenia**  
**Hyperammonemia**  
**Hyperglycinemia**

The ketoacidosis, hyperammonemia and hypoglycemia can explain the lethargy and obtundation. The ketoacidosis also produces vomiting. Mobilization of free fatty acids from stores to the liver produces a fatty liver. The increased organic acids may also be toxic to hepatocytes.

### ***PRESENTATION***

- Lethargy
- Vomiting
- Hepatomegaly
- Hypoglycemia
- Metabolic acidosis

- Hyperammonemia
- Neutropenia
- “sweaty foot” odor

There are two types of presentation, depending on the severity of the metabolic defect. The neonatal form presents within the first days of life with a life-threatening picture of severe lethargy progressing to obtundation. The infantile or late-onset form has a more insidious presentation with failure to thrive, developmental delay, and perhaps other neurologic features such as seizures and spasticity. These children can decompensate acutely during catabolic stress, usually brought on by infection. In both presentations, the pungent odor may be prominent on the body and in the blood.

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

## **ASSESSMENT**

- STAT chemstrip to check for hypoglycemia
- vital signs, cardiovascular stability
- hydration status
- presence of fever; signs of infection
- hepatomegaly
- neurologic status; evidence of increased intracranial pressure

## **LABS**

### Blood

- (arterial) blood gas
- electrolytes, measured CO<sub>2</sub>, glucose
- ammonia (in ice STAT to lab)
- AST, ALT, AlkPO<sub>4</sub>, PT, PTT
- plasma amino acids
- serum carnitine
- CBC, differential WBC count, platelets

### Urine

- urinalysis for specific gravity and ketones
- urine for organic acids
- as needed, cultures of blood, urine and throat

**NOTE, organic acids and ammonia are toxic to the brain and accumulations of these may result in cerebral edema. Caution should be exercised when considering the need for a lumbar puncture.**

## ***TREATMENT***

The treatment for acute metabolic decompensation in these disorders includes:

1. Hydration
2. Correction of the biochemical abnormalities (metabolic acidosis, hyperammonemia, hypoglycemia)
3. Reversal of catabolism/promotion of anabolism
4. Elimination of toxic metabolites
5. Treatment of the precipitating factor when possible (e.g. infection, excess protein ingestion)
6. Cofactor supplementation
7. Consider hemodialysis

### 1. HYDRATION

Intravenous fluids should be administered with enough glucose to prevent further catabolism and sufficient alkali to treat the acidosis.

Consider running 10% dextrose with a piggybacked bicarbonate infusion of 1.25-1.5X times the maintenance rate. Piggybacking allows individual adjustment/titration of the IV solutions. Add KCl if renal function is not compromised.

**Ringer's lactate should NEVER be used for fluid/electrolyte therapy in a child with a known/suspected metabolic disorder.**

### 2. CORRECTION OF BIOCHEMICAL ABNORMALITIES

(i) **Hypoglycemia** - if hypoglycemic, administer 1-2 g/kg of glucose IV STAT; follow with (at least) a 10% glucose solution

(ii) **Metabolic acidosis** - administer NaHCO<sub>3</sub> as a bolus (1 mEq/kg) if acutely acidotic with pH < 7.22 or bicarb level < 14, followed by a continuous infusion. If hypernatremia becomes a problem, reduce the rate of the Na bicarb drip; replace with K acetate.

(iii) **Hyperammonemia** - the elevated ammonia reflects a secondary inhibition of the urea cycle.

As treatment for the organic acidemia proceeds, the ammonia level should diminish. For extremely elevated ammonia (> 600 µmol/L) or persistently

elevated levels, dialysis should be considered (see Part 7).

### 3. REVERSAL OF CATABOLISM / PROMOTION OF ANABOLISM

(i) **GLUCOSE:** Catabolism can be diminished by providing large amounts of glucose (10% dextrose at maintenance or above), thereby surpassing hepatic glucose production. This therapy should be started as soon as possible after the patient presents to the emergency room.

(ii) **PROTEIN:** All natural protein (containing all amino acids) should be withheld for 48-72 hours while the patient is acutely ill.

Amino acid therapy may be very beneficial in facilitating clinical improvement but should be implemented only under the supervision of a physician/nutritionist with expertise in metabolic management. Providing an amino acid preparation which includes only "nonoffending amino acids" which are degraded by the defective biochemical pathway (i.e., avoiding leucine) during the initial crisis period may not only stimulate anabolism but help prevent significant weight loss.

If the patient is not significantly neurologically compromised, these preparations can be provided enterally. Specialized formula preparations for isovaleric acidemia provide the appropriate mix of amino acids. Where there exists a high risk for aspiration or a contraindication to enteral feeding, consideration should be given to providing a specialized parenteral amino acid solution available through specific TPN pharmacies.

(iii) **LIPID:**

Intralipid may be given to supply extra calories.

(iv) **CALORIES:**

A goal for calories during a period of decompensation, in order to support anabolism, would be about 20% greater than ordinary maintenance needs. One must remember that withholding natural protein from the diet also eliminates this source of calories and should be replaced by other dietary or nutritional sources.

(v) **INSULIN:**

Insulin is a potent anabolic hormone, promoting protein and lipid synthesis. While large scale or objective studies do not exist to prove its value in the treatment of metabolic crises, theoretically it would appear to be a useful adjunct in reversing unwanted catabolism and facilitating the uptake of offending amino acid precursors.

### 4. ELIMINATION OF TOXIC METABOLITES

Correction of acute metabolic perturbations (acidosis, hypoglycemia) may help clear some of the factors contributing to the encephalopathy associated with acute metabolic crises. However, the presence of large quantities of toxic

intermediate metabolites, believed to be toxic to the brain as well, are not cleared with glucose or bicarbonate, or rapidly with hydration. Consideration should be given to providing the means to help facilitate the excretion of these compounds:

(i) L-CARNITINE

Free carnitine levels are low in the organic acidemias because of increased esterification with organic acid metabolites. While carnitine supplementation is controversial, there are case reports where it has proven helpful during acute crises. If administered, it should be mixed in 10% glucose and run as an infusion to provide 100 mg/kg per 24 hour period (max = 5 grams/day). When oral fluids are tolerated, carnitine may be administered PO at a dose of 100 mg/kg/day.

(ii) L-GLYCINE

While glycine supplementation is controversial, it may prove helpful during acute crises for detoxifying toxic acyl-CoA accumulates. Glycine may be administered PO at a dose of 150-300 mg/kg/day.

(iii) HEMODIALYSIS:

When a patient is comatose, dialysis is indicated to facilitate a more rapid clearance of metabolic toxins which would otherwise be dependent on renal excretion, a much slower process (see 6. HEMODIALYSIS).

## 5. TREATMENT OF PRECIPITATING FACTORS

Infection should be treated vigorously when possible. Note that neutropenia (and thrombocytopenia) frequently accompany metabolic decompensation. Bone marrow recovery is expected once the levels of toxic metabolites diminish significantly

## 6. HEMODIALYSIS

Hemodialysis is indicated in cases with -

- intractable metabolic acidosis
- unresponsive hyperammonemia (> 600  $\mu\text{mol/L}$ )
- coma
- severe electrolyte disturbances (usually iatrogenic)

The Renal Service should be alerted early on in the hospital course.

## MONITORING THE PATIENT -

Clinical parameters -  
Mental status

Fluid balance  
Evidence of bleeding (if thrombocytopenic)  
Symptoms of infection (if neutropenic)

Biochemical parameters -

Electrolytes, measured CO<sub>2</sub>, glucose, ammonia, blood gases q 4-6 hours  
CBC with differential, platelets  
Urine for ketones q void; follow specific gravity

RECOVERY

The patient should be kept NPO until his/her mental status is more stable. Anorexia and nausea/vomiting during the acute crisis period makes a significant oral intake unlikely. If the patient is not significantly neurologically compromised, consideration should be given to providing the patient (PO or by NG tube) with a modified formula preparation containing all but the offending amino acids (see THERAPY, Part 3).

When the infant/child is able to take fluids orally/per ng/gastrostomy tube, please contact the Metabolism fellow/staff or the Metabolism nutritionists, since each patient has a unique, modified diet. Each day, the nurses caring for the patient should review the menu with the parents or the nutritionists to avoid dietary mistakes; these do happen and can be disastrous in the peri-crisis period.

**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.**