

ACUTE ILLNESS PROTOCOL ORGANIC ACID DISORDERS

ISOVALERIC ACIDEMIA

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 NaHCO₃ 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 $\mu\text{mol/L}$) 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 CO₂, 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.