ISOVALERIC ACIDEMIA

RECOMMENDATIONS ON EMERGENCY MANAGEMENT OF METABOLIC DISEASES

Department of Medical Genetics
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- Patient’s name:
- Date of birth:

• Please read carefully. Meticulous and prompt treatment is important as there is a high risk of serious complications.
• Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children.

INTRODUCTION

Isovaleric acidemia, an autosomal recessive, is caused by a deficiency of isovaleryl CoA dehydrogenase, an enzyme on the catabolic pathway of leucine. It is often referred to as the “sweaty foot syndrome” due to the characteristic odor body and body fluids odor produced by it. Decompensation is often triggered by metabolic stress such as fasting and/or febrile illness particularly gastro-enteritis and flu but an obvious cause is not always apparent. The central emergency features of the organic acid disorders are profound metabolic ketoacidosis and hypoglycemia. Treatment is aimed at reducing production of isovaleric and increasing its removal. The patients are treated with a low protein diet, glycine and carnitine.

PRESENTATION

The early signs of decompensation include:
- Lethargy
- Poor appetite
- Vomiting: is common and should always be taken seriously
- However, some signs may be difficult to assess such as irritability or just ‘not right’. Always listen to parents carefully; their
knowledge might exceed your expectations.
Later signs and symptoms of decompensation may include:
- Change/Altered level of consciousness
- Hypoglycemia
- Metabolic acidosis
- Hyperammonemia
- Neutropenia
- “sweaty foot” odor
- Seizures
- Hepatomegaly

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.

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.

**INITIAL MANAGEMENT IN HOSPITAL**

If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.
Management decisions should be based primarily on the clinical status. The first decision about therapy is whether the child can be treated orally or will need intravenous therapy.
• If the child is relatively well, may be treated orally but assess very carefully
• If the child is obviously unwell, must be treated with intravenous fluids.
• **If there is any doubt at all, put up an intravenous line**
• If the child is shocked or clearly very ill, arrange for admission to Intensive Care Unit

**ASSESSMENT**

**a. Clinical assessment:**
- Vital signs, cardiovascular stability
- STAT glucocheck (blood sugar) to check for hypoglycemia
- Neurologic status (including Glasgow coma score);
- Hydration status
- Presence of fever; signs of infection
- Hepatomegaly

**b. Labs:**

**Blood**
- Blood gas (arterial or venous)
- Blood glucose
- Lipase
- Ammonia
- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca²⁺, PO₄, Mg)
- Urea, creatinine
- Liver profile (including AST, ALT, AlkPO4)
- CBC differential

**Urine**
- Urine dipstick for ketones
- Urinalysis for specific gravity

**Culture**
If patient is febrile, cultures of blood, urine, and/or throat are needed depending on the patient clinical presentation.

**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. If meningitis/encephalitis is a possibility, then CT of brain should be considered before 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 dialysis

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 - 1.5 X times the maintenance rate. Piggybacking allows individual adjustment/titration of the IV solutions. Add KCL if renal function is not compromised.

- Give normal saline 10 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 ml/kg. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
- Continue with glucose 10% at 5 ml/kg/h until next solution ready. – see below
- Quickly calculate the deficit and maintenance and prepare the intravenous fluids
  - Deficit: estimate from clinical signs if no recent weight available
  - Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
  - Give 0.45% saline/10% glucose.
Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.

Recheck the electrolytes every 24 hours if still on IV fluids.

**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

a. **Hypoglycemia:** If hypoglycemic, Give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes; follow with (at least) a 10% glucose solution

b. **Metabolic acidosis:** Administer NaHCO3 as a bolus (1 mEq/kg) if acutely acidic 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.
   - If acidosis persists after correction of blood glucose and perfusion, sodium bicarbonate may be needed if the pH < 7.1 or the pH is deteriorating rapidly or the base deficit is greater than 15 mmol/l.
   - Initially give a half correction [0.15 x weight x base deficit (mmol/l)] mmol sodium bicarbonate over at least 30 minutes. 1 ml of sodium bicarbonate 8.4% contains 1 mmol but this solution should be diluted at least 1ml to 5ml of 5% glucose.

   Then review and check U&E and pH & blood gases. The acidosis normally corrects fairly quickly so that repeat doses of sodium bicarbonate should only occasionally be needed. Before doing so ask why? Is perfusion normal? What is the blood pressure, capillary refill time and urine flow? Could the patient have pancreatitis or cardiomyopathy? The treatment that will need to be considered is hemofiltration (possibly hemodialysis), assisted ventilation and inotropes.

c. **Hyperammonemia:** The elevated ammonia reflects a secondary inhibition of the urea cycle. As treatment for the organic acidemia proceeds, the ammonia level should diminish.
If hyperammonemic (> 200 μmol/l in first 24 hours or >250 μmol/l thereafter) consider N-carbamylglutamate 250 mg/kg as a single oral dose if available. Alternatively give sodium benzoate 250 mg/kg/day enterally
For extremely elevated ammonia or persistently elevated levels, dialysis should be considered (see Dialysis; Part 4-c).

3. REVERSAL OF CATABOLISM / PROMOTION OF ANABOLISM

a. **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. Hyperglycemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using local diabetic protocol for treatment of DKA rather than reducing the glucose intake. **Strict supervision is essential.**

b. **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. Provide an amino acid preparation which includes only "non-offending amino acids" (i.e., avoiding leucine) during the initial crisis period may not only stimulate anabolism but also 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.

c. **LIPID:** Intralipid may be given to supply extra calories.
d. **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.

e. **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:

a. **L-CARNITINE**

   Free carnitine levels are low in the organic acidemias. L-Carnitine should be given intravenously - 200 mg/kg/24h given as a bolus of 100 mg/kg in 30 minutes and then 50 mg/kg every 6 hours intravenously. When oral fluids are tolerated, carnitine may be administered PO at a dose of 100 mg/kg/day.

b. **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. An intravenous preparation of glycine is not normally available. If possible therefore give glycine enterally by continuous infusion via a nasogastric tube. The dose is the same as that given orally 300 mg/kg/day.
c. DIALYSIS:
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. DIALYSIS).

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. DIALYSIS
Dialysis (i.e., Peritoneal Dialysis, Hemodialysis, Continuous Renal Replacement Therapy) is indicated in cases with:
- Intractable metabolic acidosis
- Unresponsive hyperammonemia
- Coma
- Severe electrolyte disturbances (usually iatrogenic)
The Renal Service should be alerted early on in the hospital course.

MONITORING THE PATIENT
Reassess after 4-6 hours or earlier if there is any deterioration or no improvement. Clinical assessment should include:
- Mental status (Glasgow Coma Score)
- Vital signs specifically BP and temperature
- Fluid balance
- Symptoms of infection
- Evidence of bleeding (if thrombocytopenic)

Biochemical parameters:
- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca++, PO₄, Mg)
- Ammonia
- Urea, creatinine
- Blood glucose
- Blood gases
- CBC differential
- Urine for ketones and specific gravity
RECOVERY

- The patient should be kept NPO until his/her mental status is more stable.
- If the patient is not significantly neurologically compromised, enteral feeds (NG/GT) with the patient special formula containing all but the offending amino acids should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition.
- If enteral feeds cannot be introduced within 48 hours start total parenteral nutrition (TPN) early to avoid malnutrition. (Note only moderate protein restriction when using TPN is necessary. Discuss with metabolic specialist team)

ACKNOWLEDGMENT

These recommendations have been compiled by Nahya Awada, Advanced Clinical Specialist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the American College of Medical Genetics (ACMG), the British Inherited Metabolic Disease Group (BIMDG), and the New England Consortium on Metabolic Programs; and have been revised by Medical Genetics Consultants in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011

REFERENCES

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- EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) [on line], Accessed on 01 August 2011.
- Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [on line], Accessed on 01 August 2010
Dietary Emergency Protocol for

Isovaleric Acidemia (IVA)

- Name:
- Date of birth:
- Weight & date of weight measurement:

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow:
   \[ \text{Add} \quad \text{Scoops Polycose/Prophree}\] to \[\text{mls water}\]

3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
   - Small boluses: \[\text{Give} \quad \text{mls of emergency solution every} \quad \text{hour}\]
   - Or continuously if a feeding pump is available
5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   \[\text{Add} \quad \text{Scoops Polycose/Prophree}\] to \[\text{mls of Rehydration Solution}\]

6. Reassess your child every 4 hours:
   a. \[\text{Within the first 24 hours from starting the emergency regimen}:\]
      - If the child is doing well, go back to normal diet.
      - If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   b. \[\text{Between 24 – 48 hours from starting the emergency regimen}:\]
      - If your child appears well, reintroduce amino acid mix excluding natural protein source.
      - If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
c. After 48 hours from starting the emergency regimen:
   ➢ If the child is doing well and amino acid mix is well tolerated, start introducing natural protein in the diet gradually over few days starting with half amount especially if ammonia level is known to be elevated.
   ➢ If no improvement is noticed or if the child is not taking above prescribed amounts of emergency solution, **bring your child to the hospital with all medicines, special dietary products, and scoops.**

N.B:

If, **at any time from starting this emergency regimen**, your child is deteriorating and /or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

**ACKNOWLEDGMENT**

Dietary Emergency Protocols have been compiled by Eman Megdad, Metabolic Nutritionist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011