

## ISOVALERIC ACIDURIA

**Priority patient: must not wait in A&E / ED**

Patient label

If presenting with vomiting, diarrhoea or fasting  
**= Risk of hyperammonaemic coma and ketoacidosis**

**Do not wait for signs of decompensation, in all cases initiate management as set out below**

## 1 EMERGENCY WORKUP

**Urinary ketones / capillary blood ketones** (positive if >1+ or 0.8mmol/L), **blood gases, lactate, electrolytes, bicarbonate, venous glucose, calcium, ammonemia, urea (BUN), creatinine, liver function enzymes, PT, Lipase.** Add tests depending on the triggering intercurrent illness. Do not delay infusion.

## 2 TREATMENT TO BE STARTED URGENTLY, without waiting for test results

- NO natural PROTEINS or IV amino acids: **stop feeding or specific low-protein nutrition**
- If **hypovolaemia, expand** with Ringer's lactate or 0.9% NaCl **10 mL/kg** (maximum 500 mL), reassess and repeat if necessary.
- Infusion using **10% glucose** with standard electrolyte additions\* (never pure 10% glucose) + Infusion using a Y-set of **20% lipids** (e.g. Medialipids, Intralipids) via peripheral line

Age	0-24 months	2-4 years	4-14 years	> 14 years / adult	MAX INITIAL RATE
<b>Polyionic 10% glucose*</b> (glucose infusion rate)	5mL/kg/h (8mg/kg/min)	4.2mL/kg/h (7 mg/kg/min)	3.5mL/kg/h (6mg/kg/min)	2.5mL/kg/h (4mg/kg/min)	<b>120mL/h (3L/24h)</b>
<b>Lipids 20%</b>	0.4 mL/kg/h (2g/kg/day)	0.3mL/kg/h (1.5g/kg/day)	0.3mL/kg/h (1.5g/kg/day)	0.3mL/kg/h (1.5g/kg/day)	<b>20mL/h (500ml/24h)</b>

\*e.g. Polyionic, Bionolyte, B45, Glucidion, etc. if no premade solution available, use 10% glucose in water + 4g/L NaCl (70 meq/L) + 2g/L KCl (27 meq/L)

If IV line is impossible => Nasogastric tube: prepare the IV fluids listed above and pass them through the tube at the same rates.

- If there are no gastrointestinal disorders and if the preparation is available: instead of infusion, **emergency diet by continuous enteral feeding** using nasogastric tube or gastrostomy (see diet sheet from parents)
- **L-Carnitine** : **double the patient's usual dose, max 200mg/kg/day or 12g/24h**, orally every 6-8 hours or by continuous IV.
- **Oral glycine** : **double the patient's usual dose, max. 200mg/kg/day** divided into 3 or 4 doses orally or via NG tube.
- If **blood ammonia >100µmol/L** for an adult or **>150 µmol/L** for a newborn:
  - Draw a blood ammonia again and without waiting for the results treat with **N-carbamyl-glutamate** (Carbaglu): oral loading dose of 50-100 mg/kg, then maintenance dose of 50 mg/kg/6 hours orally or via NG tube (max. 8g over 24h)
  - If unavailable: **sodium benzoate** by continuous IV (orally if no IV line): loading dose of 250 mg/kg over 2h (max. 6g over 2h) then 250 mg/kg/24h (max. 12g/24h).
- **Continue** any regular treatments, but **STOP amino acid** supplements (amino acid mixtures, valine, isoleucine).
- Treat any infectious cause.

## 3 SEVERITY SIGNS = consult / transfer to Intensive Care

- **Coma or lack of neurological improvement** 3h after starting treatment
- **Haemodynamic failure**
- **Severe hyperammonaemia** (Infants > 200 µmol/L - Children and adults >150 µmol/L)
- **Ketoacidosis and severe lactic acidosis with pH < 7.10**
  - ⇒ Consider emergency haemofiltration.
  - ⇒ **Increase the concentration of the infusion** (risk of cerebral oedema) while maintaining intake of glucose, lipids and sodium [example: 30% glucose with the same glucose infusion rate as above, NaCl 6 g/L (100meq/L), potassium and calcium according to serum electrolytes + normal saline (NaCl 0.9%) in parallel with glucose solution using a Y-Set to give a total intake of **1.5 L/body surface area in m<sup>2</sup>/day** ( $Body\ surface\ area = (4 \times Weight\ in\ kg + 7) / (Weight\ in\ kg + 90)$ ).

## 4 MONITORING

- **Electrocardioscope**
- Urinalysis on every urination and/or capillary blood ketones every 6 h (positive if >1+ or 0.8 mmol/L)
- Follow-up tests (blood glucose, blood gases, lactate, electrolytes, urea (BUN), creatinine, calcium, ammonia, PT): at 4 hours if pH <7.1 and/or NH<sub>3</sub>>100µmol/L (then reassess), at 6 hours or 12 hours if pH>7.1 and NH<sub>3</sub><100µM, adjust according to context (vomiting, fever)
- Capillary blood glucose every 4h: target range 1.0-1.8g/L. If blood glucose >2g/L and glycosuria, consider insulin 0.01 IU/kg/h with subsequent dose adjustment every hour. Consider reducing sugar intake (25 to 50%) if persistent hyperglycaemia despite insulin therapy at 0.05 IU/kg/h and/or onset of raised blood lactate levels > 5mmol/L.

**PATHOPHYSIOLOGY:**

Isovaleric aciduria is an organic aciduria which exposes patients to endogenous intoxication, with **lactic and/or ketotic acidosis and hyperammonaemia** due to a deficiency in the leucine degradation pathway. This is why this patient is treated with a **low-protein diet** and with carnitine long-term.

The usual treatment is (depending on the patient):

- Oral carnitine (Levocarnil®) and glycine (Glycocolle®) supplementation.
- Low-protein diet: more or less strict depending on age (fruit and vegetables). See "Maintenance diet" sheet. This type of diet totally excludes meat, fish and eggs.

**CIRCUMSTANCES WITH RISKS OF DECOMPENSATION:**

- Intercurrent infectious disease, fever, anorexia, vomiting, surgery, excess protein intake, **or any fasting state, insufficient caloric intake, weight loss or catabolic state.**
- **In all these situations, the patient must be kept in hospital** because the acidosis and hyperammonaemia can worsen very rapidly. **They represent an emergency:** do the workup on the patient in A&E before admitting him/her to the ward. **ACT QUICKLY** to prevent severe acidosis and multiorgan failure.

**CLINICAL SIGNS OF DECOMPENSATION: Do not wait for these signs!**

- **Acute neurological disorders** (altered mental status, confusion, drowsiness, gait disorder, hallucinations, behavioural disorders, tremors, abnormal movements, etc.), transient blindness.
- **Gastrointestinal signs** (vomiting, anorexia, nausea, etc.), dehydration.
- **Haemodynamic failure.**
- **Pancreatitis**

**DRUG CONTRAINDICATIONS / GENERAL ADVICE:**

**Prohibited:** valproic acid (depakin®, etc.). Corticosteroid therapy: consider the need if duration > 3 days. Use hydrocortisone if necessary in intensive care.

- All vaccinations are recommended (particularly influenza).
- Prolonged fasting is contraindicated, never leave the patient without a supply of carbohydrate (infusion or continuous enteral feeding) or carnitine.
- **Do not leave the patient without proteins for more than 3 days.** Do not forget vitamins and trace elements when intake is exclusively parenteral. The emergency treatment should be reassessed with the metabolism clinician during the day.
- **In case of admission to hospital** (or attendance at A&E): patients must take with them their usual treatments and the special products that they have in order to prepare an emergency diet.

**SURGERY under General Anaesthesia:**

**WARNING: never leave the patient fasting without an infusion. Implement the emergency protocol with infusion as above, in preparation for surgery.**

**ASSISTANCE WITH PRACTICAL ADMINISTRATION OF TREATMENTS:**

- LEVOCARNIL IV (vial 1g = 5mL), given neat or diluted in normal saline, using a Y infusion set.
- LEVOCARNIL orally (vial 1g = 10ml), divided into 3 to 4 oral doses/day.
- SODIUM BENZOATE IV: (vial 1g=10mL), to be diluted 1:1 by volume in 10% glucose. Contains 7 mEq of sodium per gram of benzoate.
- Carglumic acid (CARBAGLU®) 1 tablet = 200mg. Orally or via gastric tube diluted in 10 mL of water.
- L-Glycine (GLYCOCOLLE®) 1 tablet = 190mg or capsules prepared in the pharmacy specifically for the patient. Orally or via gastric tube diluted in 10 mL of water.

**ASSISTANCE WITH DIET:**

- If exceptionally a feeding bottle / meal is missed during a hospital stay: give an emergency, protein-free meal (low-protein pasta, low-protein bread with butter and jam) or, if by bottle: PFD1® / Energivit®: 1 measuring spoon per 30 mL of water (0.7 kcal/mL)
- If the composition of the ongoing emergency diet is unknown: prepare an isocaloric solution with [100g of PFD1® or Energivit® or Duocal® + 430mL of water] or [80g of maltodextrin + 20mL of oil + 425 mL of water]: equivalent preparations 500mL = 500kcal, adjust total intake according to the patient's needs. Review during working hours with a dietician, especially for calcium and electrolyte (Na, K etc.) intake.

**REFERENCE PHYSICIANS AND CONTACT DETAILS**

On-call telephone numbers for metabolic emergencies of:

At night, only the medical teams can call in emergency situations and only if the emergency certificate has not been understood or if the clinical state or test results are worrying. As far as possible make calls before night-time.

Secretarial issues must be dealt with the outpatient office during the week or by email addressed to the patient's referring metabolic physician.

Certificate issued on : Dr