ORGANIC ACIDURIAS = METHYLMALONIC ACIDURIA (MMA) or PROPIONIC ACIDURIA (PA)

Patient label

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

If presenting with vomiting, diarrhoea, fever or fasting state:
= Risk of hyperammonaemic coma, ketoacidosis and stroke-like episode

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, blood glucose, calcium, ammonemia, urea (BUN), creatinine,** liver function enzymes, **PT,** Lipase. FBC-platelets. Infectious workup. ECG
Do not delay infusion.
If possible: plasma methylmalonic acid, plasma aminoacids (quantitative) and urinary organic acids to be sent during working hours.

2 TREATMENT TO BE STARTED URGENTLY, without waiting for lab 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) if no cardiac signs - reassess and repeat if necessary.
- Infusion using **10% glucose** with standard electrolyte additions* (never pure 10% glucose/dextrose in water)

\+ Infusion using a Y-set of **20% lipids** (e.g. Medialipid, Intralipid) on a peripheral line:

Age	0-24 months	2-4 years	4-14 years	> 14 years / adult	MAX INITIAL RATE
Polyionic 10% glucose* (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)	**120mL/h (3L/24h)**
Lipids 20%	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)	**20mL/h (500mL/24h)**

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 impossible => Nasogastric tube: prepare the IV fluids listed above and pass them through the tube at the same rate

- If there are no gastrointestinal disorder 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 if vomiting.
- **For B12-responsive MMA:** give **vitamin B12 1mg/day IM or IV daily** (usual treatment B12 daily by mouth or IM injections)
- If **blood ammonia >100µmol/L** (or **>150 µmol/L** for a newborn):
  - Draw blood ammonia again and without waiting for the results: administer **N-carbamyl-glutamate** (Carbaglu): oral loading dose 50-100 mg/kg followed by maintenance dose 50 mg/kg/6h orally or via NG tube (max. 8g over 24h).
  - If unavailable: **sodium benzoate** by continuous IV (or oral if no IV access): loading dose of 250 mg/kg over 2h (max. 6g over 2h) then 250 mg/kg/24h (max. 12g/24h).
- **Continue** any regular treatments, including **ammonia scavengers** (Carbaglu®, sodium benzoate) but **STOP aminoacids** 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,** cardiac rhythm disorder (risk of QTc prolongation or heart failure for PA patients).
- **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 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/m² of BSA/day** *(Body surface area = (4 x Weight in kg + 7) / (Weight in kg + 90))*

4 MONITORING

- **Electrocardioscope, daily ECG -** Echocardiogram during working hours if propionic acidaemia in case of severe decompensation.
- Urinanalysis on every urination and/or capillary blood ketones (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 NH3>100µmol/L (then reassess), at 6 hours or 12 hours if pH>7.1 and NH3<100, 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 (25-50%) if persistent hyperglycaemia despite insulin therapy at 0.05 IU/kg/h and/or onset of hyperlactataemia > 5 mmol/L.

PATHOPHYSIOLOGY:

Organic acidurias (MMA, PA) expose patients to a risk of endogenous intoxication, with **ketotic and/or lactic acidosis and hyperammonaemia,** through breakdown of certain amino acids and other molecules such as odd-chain fatty acids. The usual treatment is (depending on the patient):

- Oral carnitine (Levocarnil®).
- Limitation of fasting time with enteral feeding at night in children.
- An extremely strict low-protein diet: This type of diet completely excludes meat, fish and eggs, with other foodstuffs being allowed only in carefully measured amounts. See "Maintenance diet" sheet.
- Some patients receive ammonia chelators: N-carbamyl-glutamate or sodium benzoate.

These patients are at risk of **hypocalcaemia**, **acute pancreatitis** and **pancytopenia** in cases of severe decompensation.
Patients with **propionic acidaemia** are at risk of cardiomyopathy with **cardiac rhythm disorders** and **QT prolongation**.

Patients with **methylmalonic acidaemia** are at risk of **renal failure** and tubulopathy**.**

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!

- **Metabolic acidosis with Kussmaul dyspnea.**
- **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, **pancreatitis**.
- Cardiac rhythm disorders, **haemodynamic insufficiency.**
- **Pancytopenia, hypocalcaemia.**

Prohibited: valproic acid (depakin®, etc.). Corticosteroid therapy: consider need if duration > 3 days. Use hydrocortisone if necessary in intensive care. For PA patients: **beware of drugs causing QT prolongation.**

- 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 will be reassessed with the metabolic medicine specialist 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 / SAMPLING:

- L CARNITINE IV (vials 1g = 5mL), given neat or diluted in normal saline, using a Y infusion set.
- L CARNITINE orally (vials 1g = 10mL), divided into 3 to 4 doses/day.
- SODIUM BENZOATE IV (vials 1g = 10mL), to be diluted 1:1 by volume in 10% glucose. Contains 7 mEq Na per gram of benzoate.
- Carglumic acid (CARBAGLU®) 1 tablet = 200mg. Orally or via gastric tube diluted in 10 mL of water.
- Vitamin B12 (cyanocobalamin or hydroxocobalamin): 1mg IM. Can be given IV diluted in at least 20 mL (slow IV over 1h)

Samples for biochemistry: Plasma MMA (methylmalonic acid) and Plasma amino acids: heparin tube with green stopper. At night and weekends, centrifuge and freeze the plasma. Urinary organic acids: 1 urine sample. Send to specialist biochemistry laboratory during working hours.

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 DOCTORS 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