EMERGENCY CERTIFICATES - G2M NETWORK

V1 – May 2022

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

Label

Priority patient: must not wait in A&E

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

Urinary ketones / capillary blood ketones (positive if >1+ or 0.8mmol/L), **ABG, lactate, electrolytes, bicarbonate, blood glucose, calcium, ammonia, urine acids, creatinine,** liver function tests, **PT,** Lipase. FBC-platelets. Infectious workup: ECG (risk of QT prolongation). Do not delay infusion.

If possible: Plasma MMA and amino acid chromatography, urinary organic acid chromatography, to be sent during working hours (see overleaf for technical details).

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

- NO IV amino acids or proteins by mouth: **stop feeding or specific low-protein nutrition**
- If **hypovolaemia, replenish** with Ringer's Lactate or 0.9% NaCl at **10 ml/kg** (maximum 500 ml) if no cardiac signs - reassess and continue if necessary.
- Infusion using **10% glucose** with standard electrolyte additions* (not pure 10% glucose)

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

Age	0-24 months	2-4 years	4-14 years	> 14 years / adult	MAX FLOW RATE
10% glucose + added electrolytes*	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 solutes available, 10% glucose + 4g/L of NaCl (70 meq/L) and 2g/L of KCl (27 meq/L)

If unable to infuse the patient => Nasogastric tube: prepare the IV fluids listed above and pass them through the tube at the same rate

- 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 (preparation known to the parents from the diet sheet)
- **L-Carnitine (Levocarnil): double the patient's usual dose, max 200mg/kg/day not exceeding 12g/24h,** orally every 6-8 hours or continuous IV if vomiting.
- **For B12-responsive MMA:** give vitamin **B12 1mg/day IM or IV every day** (usual treatment B12 daily by mouth or by spaced IM injections)
- If **blood ammonia >100µmol/L** in a child / adult or **>150 µmol/L** in a newborn:
  - Check again and without waiting for the results: **Carbaglu®** (N-carbamyl-glutamate): oral loading dose 50-100 mg/kg then maintenance dose 50 mg/kg/6 hours orally or via NG tube (Max. 8g over 24h)
  - If not available: **Sodium benzoate** by continuous IV (oral if no IV line): Start with a **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 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 insufficiency,** 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 in quantity sufficient for same glucose intake 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/day** *(Body surface area = (4 x W + 7) / (W + 90))*

4 MONITORING

- **Electrocardioscope, ECG every 24 h -** Echocardiogram during working hours if propionic acidaemia in cases of severe decompensation.
- Urine analysis on every urination and/or capillary blood ketones (positive if >1+ or 0.8 mmol/L)
- Follow-up tests (blood glucose, ABG-lactate, electrolytes, urea, 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 4 h: target 1 to 1.8g/L. If blood glucose >2g/L and glyosuria, consider insulin 0.01IU/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 **ketoacidosis, lactic acidosis and hyperammonaemia,** through breakdown of certain amino acids and other molecules such as odd-chain fatty acids. The normal treatment is (depending on the patient):

- Oral carnitine (Levocarnil®) treatment.
- 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: Carbaglu® 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 IN WHICH THERE IS A RISK OF DECOMPENSATION:

- Intercurrent infectious disease, fever, anorexia, vomiting, surgery, excess protein intake, **or any fasting state, calorie deficiency, 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 hospital. **ACT QUICKLY** to prevent severe acidosis and multiorgan failure.

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

- **Metabolic acidosis and acidotic hyperventilation**
- **Acute neurological disorders** (disorders of alertness, confusion, drowsiness, problems with balance, 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: weigh up the need if duration > 3 days. No bar to using hydrocortisone hemisuccinate 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:

- LEVOCARNIL IV (amp. 1g = 5ml), given neat or diluted in normal saline, using a Y infusion set.
- LEVOCARNIL orally (amp. 1g = 10ml), divided into 3 to 4 oral doses/day.
- SODIUM BENZOATE IV: [Sodium benzoate AP-HP 1g-10mL]; ampoule 1g = 10ml, to be diluted 1:1 by volume in 10% glucose. Contains 7 meq of sodium per gram of benzoate. Status = hospital preparation
- Carglumic acid (CARBAGLU®) 1 tablet = 200mg. Orally or via gastric tube diluted in 10 mL of water. No Temporary Use Authorisation needed, available in hospital pharmacy.
- 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 AAC (amino acid chromatography): heparin tube with green stopper. At night and weekends, centrifuge and freeze the plasma. Urinary OAC (organic acid chromatography): 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 not known: 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 via the medical secretariat during the week or by email addressed to the patient's referring metabolic doctor.
Certificate issued on Dr