Lysinuric protein intolerance (LPI) (urea cycle disorder)

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

Patient label

If presenting with vomiting, diarrhoea or fasting state:
Risk of hyperammonaemic coma

1 EMERGENCY WORKUP

Blood ammonia (NH3), liver enzymes, PT, serum electrolytes, urea (BUN), creatinine, blood glucose, FBC, ferritin, fibrinogen, triglycerides, LDH, lipase, amylase. + Tests depending on triggering intercurrent illness. Do not delay infusion.

2 TREATMENT TO BE STARTED URGENTLY, without waiting for lab results

A- In all cases

- NO IV amino acids or proteins by mouth: **stop feeding or specific low-protein diet.**
- Do not give IV lipids initially, reassess during working hours with the metabolic medicine specialist in light of test results.
- **Infusion** using **10%** glucose with standard electrolyte additions* (never pure 10% glucose)

Age	0-24 months	2-4 years	4-14 years	> 14 years / adult	MAX FLOW RATE
Polyionic 10% glucose* (glucose infusion rate)	6mL/kg/h (10mg/kg/min)	5mL/kg/h (8mg/kg/min)	3.5mL/kg/h (6mg/kg/min)	2.5mL/kg/h (4mg/kg/min)	**120mL/h (3L/24h)**

e.g.: Bionolyte®, Glucidion®, etc. if no pre-made 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 or gastrostomy: 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 (preparation known to the parents from the diet sheet)
- **Continue** usual treatment with:
  - **Sodium benzoate** (oral or IV if vomiting): 100 to 400 mg/kg/day without exceeding 12g/24h.
  - And/or **Sodium phenylbutyrate** : Ammonaps®, Ravicti®, Pheburane® by oral route only: 100 to 400 mg/kg/day each, without exceeding 16g/24h.
  - For the other treatments, if unavailable, reassess during working hours (arginine, citrulline etc.)

B- If neurological signs, without waiting for blood ammonia result, or if blood ammonia level > 100 µmol/L

- **Continuous IV sodium benzoate**: Start with a **loading dose** of 250 mg/kg over 2 hours (**max. 8g over 2h**) then 250 to 500 mg/kg/24h (**max. 12g/24h**) (can be given via NG tube if no IV access). Draw another blood ammonia sample before giving the loading dose, without waiting for the results.

3 OTHER POTENTIAL RISKS

Lysinuric protein intolerance also exposes patients to a risk of other intercurrent diseases, which should be investigated depending on the clinical signs: **pancreatitis**, **respiratory disorders** (decompensated alveolar proteinosis / pulmonary fibrosis), haematological disorders (**macrophage activation syndrome**), **renal failure,** etc. These pathologies must be managed with adapted care, not related specifically to LPI, with referral from dedicated specialists if necessary.

4 SEVERITY SIGNS = Refer / Transfer to Intensive Care

- **Coma** or **lack of neurological improvement** 3h after starting treatment.
- and/or **Severe hyperammonaemia (Infants > 200 µmol/L - Children and adults >150 µmol/L)**
- and/or rarely, severe hepatic insufficiency: Prothrombin ratio < 30%, factor V < 50%
  - **Start Sodium phenylacetate** Ammonul® 250 mg/kg/day, ideally via central line, max 12g (stop benzoate and phenylbutyrate)
  - While waiting, consider a complementary loading dose of Sodium phenylbutyrate = Ammonaps: 250mg/kg orally (max. 10g).
  - **Consider haemodialysis.**
  - **Increase infusion concentration** (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 of body surface area/day** *(Body surface area = (4 x Weight in kg + 7) / (Weight in kg + 90))*
  - *In intensive care: Neuroprotective measures and prevention of secondary brain damage*
  - Arginine hydrochloride IV (only if oral route impossible): 250 mg/Kg/24h (max 12g/24h).

5 MONITORING

- Follow-up tests (NH3, PT, serum electrolytes): at 4 hours if NH3>100 µmol/L (then reassess), at 6 hours or 12 hours if NH3 < 100 µmol/L depending on context (vomiting, fever). Tests for macrophage activation syndrome or others depending on the initial results.
- Capillary blood glucose every 4 h: target 1 to 1.8g/L. If blood glucose > 2g/L with 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 > 3 mmol/L.

PATHOPHYSIOLOGY:

Lysinuric protein intolerance exposes the patient to a risk of endogenous intoxication by ammonia produced by the breakdown of amino acids from proteins. There is also a risk of **macrophage activation syndrome**, alveolar proteinosis and/or **pulmonary fibrosis**, **renal failure** and **acute pancreatitis**. The usual oral treatment is the same as for hyperammonaemia (depending on the patient):

- Sodium benzoate and/or Phenylbutyrate (Ammonaps®, Ravicti®, Pheburane®): 100 to 300 mg/kg/day of each divided into 2 to 4 doses.
- Citrulline and/or arginine [except in arginase deficiency]: 100 to 300 mg/kg/day of each divided into 2 to 4 doses.
- An extremely strict low-protein diet: see "maintenance diet" sheet. For the most severe forms, meat, fish, eggs, dairy products and cereals are prohibited. Fruit and vegetables are allowed in measured and weighed quantities. Dietary supplements: low-protein products, mixtures of vitamins and minerals.

CIRCUMSTANCES WITH A RISK 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 hyperammonaemia can worsen very rapidly. **They are an emergency:** do the workup on the patient in A&E before admitting him/her to the ward. **ACT QUICKLY,** to prevent severe hyperammonaemia and its neurological sequelae: the intensity and duration of the ammonia level peak determines the neurological prognosis.

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

- Acute neurological disorders (altered mental status, confusion, drowsiness, balance disorder, ataxia, behavioural disorders, tremors, abnormal movements, etc.).
- Or gastrointestinal signs (vomiting, anorexia, nausea etc.).
- **Will progress to coma +/- convulsions and death, or serious neurological sequelae if treatment is not started rapidly.**

DRUG CONTRAINDICATIONS / GENERAL ADVICE:

Prohibited: acetyl salicylic acid (aspirin), 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 chelators.
- **Do not leave the patient without proteins for more than 3 days.** Do not forget vitamins and trace elements when parenteral nutrition used exclusively; 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 their special products 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 overleaf, in preparation for surgery.

ASSISTANCE WITH PRACTICAL ADMINISTRATION OF TREATMENTS:

- SODIUM BENZOATE IV: vials 1g=10mL, to be diluted 1:1 by volume in 10% glucose. Contains 7 mEq of sodium per gram of benzoate.
- SODIUM PHENYLACETATE AMMONUL®: Recommended via central line. Use a 0.22µm filter. 50 mL=5g of sodium benzoate and 5g of sodium phenylacetate. Dilute in 10% glucose to obtain a concentration of 10 mg/mL. Contains 13.3 mEq of sodium per 10 mL.
- ARGININE IV (only if oral or enteral administration is impossible) :
  - Dosage at 6.25%: possible via peripheral venous line.
  - Dosage at 21%: possible via central line. Dilute in 5% glucose or NS to obtain a concentration of arginine < 100 mg/mL.

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