EMERGENCY CERTIFICATES - G2M NETWORK

V2 – Sept 2024

UREA CYCLE DISORDERS

(OTC deficiency, CPS deficiency, type 1 citrullinaemia, argininosuccinic aciduria, arginase deficiency,

PRIORITY PATIENT: MUST NOT BE KEPT WAITING IN THE EMERGENCY DEPARTMENT

In the event of vomiting, diarrhoea, fever or fasting
= Risk of hyperammonaemic coma

Label

Do not wait for signs of decompensation; always initiate the following management protocol

Phone call only if the emergency certificate is not understood.

1 EMERGENCY ASSESSMENT

Blood ammonia, liver function tests, PT, serum electrolytes, blood glucose, blood gases, lactate. Further tests depending on the intercurrent illness triggering the episode. Do not delay infusion.

2 START TREATMENT URGENTLY, without waiting for test results

A. Sodium benzoate = Emergency ammonia scavenger

- **If neurological signs are present, without waiting for blood ammonia results, or if blood ammonia > 100 µmol/L:** **Sodium benzoate** by continuous IV infusion Start with a **loading dose** of 250 mg/kg over 2 hours (**max 8 g over 2 hours**), then 250–500 mg/kg/24h (**max 12 g/24h**) (switch to PO via NG tube if no other route is available). Take ammonia level just before the loading dose and administer without waiting for the result.
- **In the absence of neurological signs or if blood ammonia < 100 µmol/L**: **continue Benzoate at the usual dose** (PO or IV if vomiting): 100–400 mg/kg/day, not exceeding 12 g/24h

B. Emergency infusion or emergency diet/enteral nutrition: systematic, regardless of neurological examination or blood ammonia level

- NO IV amino acids or oral proteins: **stop feeding or use a specific low-protein diet.**
- **Infuse 10% glucose** with standard electrolyte supplementation* (not 10% glucose alone)

+ Y-site infusion of **20% lipids** (e.g. Medialipids, Intralipids) via a peripheral line:

Age	0 - 24 months	2 - 4 years	4 - 14 years	> 14 years/adult	MAX. FLOW RATE
10% glucose solution + added electrolytes*	6 mL/kg/h (10 mg/kg/min)	5 mL/kg/h (8 mg/kg/min)	3.5 mL/kg/h (6 mg/kg/min)	2.5 mL/kg/h (4 mg/kg/min)	120 mL/h (3L/24h)
20% lipids	0.4 mL/kg/h (2 g/kg/day)	0.3 mL/kg/h (1.5 g/kg/day)	0.3 mL/kg/h (1.5 g/kg/day)	0.3 mL/kg/h (1.5 g/kg/day)	20 mL/h (500 mL/24h)

e.g.: G10 balanced electrolyte solution, G10 Bionolyte, G10 Glucidion. If unavailable: 10% glucose + 4 g/L NaCl (70 mEq/L) and 2 g/L KCl (27 mEq/L)

If IV infusion is not possible *=> Nasogastric tube: prepare the above IV solutions and administer via the tube at the same rates, each via a Y-set*

- **Emergency diet:** In the absence of gastrointestinal issues and if dietary preparation is available: instead of infusion, continuous enteral feeding through a nasogastric tube or gastrostomy (preparation known to parents according to the dietary sheet)

C. Other oral ammonia scavengers. Continue usual treatments:

- **Ammonaps®**, Ravicti®, Pheburane® PO only: 100–400 mg/kg/day each, max 16 g/24h
- For other treatments (arginine, citrulline, etc.), if not available, review during business hours

D. Possible hypokalaemia in argininosuccinic aciduria (e.g. cramps, fasciculations, trismus, paralytic ileus)

3 SIGNS OF SERIOUS ILLNESS = Specialist opinion/transfer to

Refer to the Emergency section on

- **Coma** or **no neurological improvement** 3 hours after starting treatment
- and/or **severe hyperammonaemia (Infants > 200 µmol/L - Children & Adults > 150 µmol/L)**
- and/or **severe hepatic failure**
  - **Start Ammonul®** 250 mg/kg/day (stop Benzoate and Phenylbutyrate), preferably via CVC, max 12 g
  - In the meantime, option of giving an additional loading dose of Ammonaps: 250mg/kg orally (max. 10g).
  - **Consider haemodialysis:** continue for at least 12 h to avoid rebound (no intermittent dialysis)
  - **Insert a central line to deliver concentrated infusion** (risk of cerebral oedema) while maintaining carbohydrate, lipid and sodium intake [example: 30% glucose (enough to provide the same carbohydrate intake as above), NaCl 6 g/L (100 mEq/L), potassium and calcium according to electrolytes + 0.9% sodium chloride in Y with glucose infusion, for a total of **1.5 L/m²/day** *(Body surface area = (4W + 7)/(W + 90)].*
  - *In ICU: Measures for neuroprotection and avoiding secondary insults to the brain of systemic origin*
  - Arginine hydrochloride IV (only if PO not possible): 250 mg/kg/24h (max 12g/24h) (contraindicated in arginase deficiency).

4 MONITORING

- Check test results (NH_3, PT, electrolytes): at the end of the Benzoate loading dose, then every 6 h if initial hyperammonaemia.
- If NH_3 < 100 µmol/L: monitor between H6 and H12 depending on context (vomiting, fever).
- Correct hypokalaemia (argininosuccinic aciduria).
- Capillary blood glucose every 4 h: target 1–1.8 g/L. If BG > 2 g/L and glycosuria is present, consider insulin 0.01 IU/kg/h, adjusted hourly. Consider reducing sugar intake (25–50%) if hyperglycaemia persists despite insulin 0.05 IU/kg/h and/or if hyperlactataemia > 3 mmol/L occurs.

UREA CYCLE DISORDERS

PATHOPHYSIOLOGY:

Urea cycle disorders expose the patient to endogenous intoxication by ammonia produced by the breakdown of amino acids that make up proteins.

Usual oral treatment may include (depending on patient):

- Sodium benzoate and/or Phenylbutyrate (Ammonaps®, Ravicti®, Pheburane®): 100 to 300 mg/kg/day for each in 2 to 4 doses.
- Citrulline (depending on the deficiency) and/or arginine [except for arginase deficiency]: 100 to 300 mg/kg/day for each in 2 to 4 doses.
- Extremely strict low-protein diet. For the most severe forms: no meat, fish, eggs, dairy products or cereals; fruit and vegetables allowed in measured and weighed quantities, dietary supplements (low-protein foods, vitamin and mineral mixtures).

SITUATIONS WITH RISK OF DECOMPENSATION:

- Intercurrent infection, fever, anorexia, vomiting, surgery, excessive protein intake, **any state of fasting, calorie deficiency, weight loss or catabolism.**
- **In all these situations, the patient must be kept in hospital,** as hyperammonaemia can worsen very quickly. **This is an emergency**: stabilise the patient in the ED before transfer to hospital. **ACTING QUICKLY** can prevents severe hyperammonaemia and neurological sequelae: the intensity and duration of the peak in blood ammonia levels determine the neurological prognosis.

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

- Acute neurological symptoms (impaired alertness, confusion, drowsiness, balance disorders, ataxia, behavioural disorders, tremors, abnormal movements, etc.).
- Or gastrointestinal symptoms (vomiting, anorexia, nausea, etc.).
- **Progression to coma +/- seizures and death or severe neurological sequelae if treatment is not initiated promptly.**

DRUG CONTRAINDICATIONS / GENERAL ADVICE:

Prohibited: acetylsalicylic acid (aspirin), valproic acid (Depakine®, etc). Corticosteroid therapy: weigh up the indication if duration > 3 days; no restriction on the use of hydrocortisone hemisuccinate if resuscitation is required.

- All vaccinations are recommended (particularly influenza).
- Prolonged fasting contraindicated: never leave patient without carbohydrate intake (infusion or continuous enteral tube feeding) nor scavengers
- Remember vitamin and trace element supplementation if the patient is on exclusive parenteral nutrition. **Do not leave the patient without protein intake for more than 3 days.** Emergency treatment to be reviewed with the metabolic specialist during the day.
- **In the event of hospitalisation** (or emergency consultation): patients must bring their usual treatments and any special products they have with them to prepare an emergency diet.
- Phenylbutyrate (Ammonaps®, Ravicti®, Pheburane®) is contraindicated during pregnancy.
- Risk of hypokalaemia in cases of argininosuccinic aciduria.

SURGERY with General Anaesthesia:

CAUTION: never leave the patient fasting without an infusion. Apply the emergency protocol with the above infusion in preparation for surgery and continue until normal feeding resumes (in consultation with the specialist centre).

GUIDANCE ON PRACTICAL ADMINISTRATION OF TREATMENTS:

- SODIUM BENZOATE IV: [Sodium benzoate AP-HP 1 g–10 mL]; ampoule 1 g = 10 mL, to be diluted volume for volume in 10% glucose. Contains 7mEq sodium per gram of benzoate. Status = hospital preparation.
- AMMONUL®: Recommended for administration via central line. Use a 0.22 µm filter. 50 mL bottle = 5 g sodium benzoate and 5 g sodium phenylacetate. Dilute in 10% glucose solution to obtain a concentration of 10 mg/mL. Contains 13.3 mEq sodium per 10 mL of product. Available in emergencies. Compassionate use authorisation (CUA, formerly 'named-patient ATU').
- IV ARGININE (only if oral or enteral administration is not possible):
  *Dosage at 6.25% [Arginine hydrochloride AP-HP 6.25%]: possible via peripheral IV. Status: hospital preparation, no CUA.
  *Dosage at 21% [L-Arginine hydrochloride 21% B.BRAUN]: via central venous catheter (CVC). Dilute in 5% glucose solution or saline to obtain a concentration of arginine below 100 mg/mL. Compassionate use authorisation (CUA, formerly 'named-patient ATU').

GUIDANCE ON DIET:

- If, exceptionally, a feed/meal is missed during hospitalisation: give an emergency protein-free meal (low-protein pasta, low-protein bread with butter and jam) or, for infants: PFD1®/Energivit®: 1 measuring spoon per 30 mL water (0.7 kcal/mL).
- If the composition of the continuous emergency diet is unknown: prepare an isocaloric solution with [100 g PFD1®, Energivit® or Duocal® + 430 mL water] or [80 g maltodextrin + 20 mL oil + 425 mL water]: equivalent preparations 500 mL = 500 kcal. Adjust total intake to the patient's needs. To be reviewed with a dietitian during working hours, particularly for calcium and electrolyte intake (Na, K, etc.).

REFERRING PHYSICIANS AND NUMBERS:

At night, only medical teams may call in emergencies and only if the emergency certificate is not understood or if the clinical condition or test results are concerning. Whenever possible, calls should be made before nightfall.
Secretarial issues must be dealt with via the medical secretariat during the week, or by email addressed to the patient's metabolic medicine specialist.

Certificate issued on Dr