UREA CYCLE DISORDERS

(OTC deficiency, CPS deficiency, citrullinaemia type 1, argininosuccinic aciduria, arginase deficiency, HHH syndrome)

Priority patient: must not wait in A&E

Label

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

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

1 EMERGENCY WORKUP

Plasma ammonia concentration, liver function tests, PT, serum electrolytes, blood glucose, ABG, lactate. Tests depending on triggering intercurrent illness. Do not delay infusion.

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

A. Management in all cases

- NO IV amino acids or proteins by mouth: **stop feeding or specific low-protein nutrition**
- **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*	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)**
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 G10, Bionolyte G10, Glucidion G10… if solutions not available, 10% glucose + 4g/L NaCl (70mEq/L) and 2g/L KCl (27mEq/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 in each branch of the Y-Set*

- If there are no gastrointestinal disorders and if the preparation is available: instead of infusion, **emergency diet** by continuous enteral feeding using a nasogastric tube or gastrostomy (preparation known to the parents from the diet sheet)
- **Continue** usual treatment with:
  - **Sodium benzoate** (orally or IV if vomiting or neurological signs): 100 to 400 mg/kg/day without exceeding 12g/24h
  - and/or **Ammonaps®**, Ravicti®, Pheburane® by oral route only: 100 to 400 mg/kg/day each, without exceeding 16g/24h
  - For the other treatments, if not available, review in working hours (arginine, citrulline etc.)

B. If neurological signs and/or vomiting, 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**) (given orally via NG tube if no infusion line set up). Take a check sample for blood ammonia concentration before giving the loading dose, and **sodium benzoate administration** without waiting for the result.

3 SEVERITY SIGNS = Consult / 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 **Severe hepatic insufficiency:** Prothrombin ratio < 50%, factor V < 30%
  - **Start Ammonul®** (250 mg/kg/day) (stop benzoate and phenylbutyrate), ideally via a central line, max. 12g
  - While waiting, consider a complementary loading dose of Ammonaps: 250mg/kg orally (max. 10g).
  - **Consider haemodialysis**
  - **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))*
  - *In intensive care: Neuroprotective measures and prevention of secondary brain damage*
  - Arginine hydrochloride IV (only if oral route not possible): 250 mg/Kg/24h (Max. 12g/24h) – (! contraindicated if arginase deficiency).

4 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)
- 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 to 50%) if persistent hyperglycaemia despite insulin therapy at 0.05 IU/kg/h and/or onset of hyperlactataemia > 3mmol/L

This emergency protocol is proposed by the G2M network working group. The protocol may be modified under the responsibility of the referring doctor. In no circumstances does it replace the responsibility of the doctor treating the patient in A&E.

PATHOPHYSIOLOGY:

Urea cycle disorders expose the patient to a risk of endogenous intoxication by the ammonia produced by the breakdown of amino acids contained in proteins.

The usual oral treatment can be (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 (depending on the disorder) 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. For the most severe forms: meat, fish, eggs, dairy products and cereals are not allowed, fruits and vegetables are allowed in measured and weighed quantities, plus dietary supplements (low-protein products, mixtures of vitamins and minerals).

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 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 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 (disorders of alertness, confusion, drowsiness, problems with balance, 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: weigh up the need if duration > 3 days. No bar to using hydrocortisone hemisuccinate 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 forget vitamins and trace elements when intake is exclusively parenteral. **Do not leave the patient without proteins for more than 3 days.** 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.

°Phenylbutyrate (Ammonaps®, Ravicti®, Pheburane®) Ravicti® is contraindicated during pregnancy.

°Risk of hypokalemia in case of argino-succinic acciduria.

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, and continue until appropriate nutrition has been resumed (consult with referring service)

ASSISTANCE WITH PRACTICAL ADMINISTRATION OF DRUGS:

° 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

° AMMONUL®: Recommended via central line. Use a 0.22µm filter. 50 ml bottle = 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 of product. Available for emergency use. Status: Compassionate Use Authorisation (CUA) (formerly nominative Temporary Use Authorisation).

° ARGININE IV (only if oral or enteral administration is not possible):

*Dosage at 6.25% [Arginine (hydrochloride) AP-HP 6.25%]: possible via peripheral venous line. Status: hospital preparation, no CUA

*Dosage at 21% [L-Arginine hydrochloride 21% B.BRAUN]: via central line. Dilute in 5% glucose or normal saline to obtain a concentration of arginine less than 100 mg/ml Status: CUA

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.