Carbonic anhydrase deficiency

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

Patient Label

If presenting with vomiting, diarrhea or fasting state:

Risk of hyperammonaemic coma and ketoacidosis

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

1 EMERGENCY WORKUP

Blood gases, lactate, electrolytes, bicarbonate, ammonaemia (NH3), urea (BUN), creatinine, liver enzymes, **PT**, + Tests in line with triggers and/or intercurrent illness. Must not delay treatment.

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

- NO IV or ORAL aminoacids / proteins: **stop feeding or specific low-protein diet.**
- Infusion using **10% glucose (dextrose) in water** with standard electrolyte additions* (never 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 INITIAL 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)
20% Lipid	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.: Bionolyte®, Glucidion®, etc. if no pre-made solution available, use 10% glucose in water + 4 to 6g/L NaCl (70mEq/L) + 2g/L KCl (27mEq/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 in each branch of the Y-set.

- Continue usual treatments.
- **If neurological signs, without waiting for ammonaemia result, or if ammonaemia > 100 µmol/L:**
  - If available, **ideally carglumic acid (Carbaglu®)**: loading dose 50mg/kg then maintenance dose 100mg/kg/day divided into 4 oral doses (max. 8g over 24h)
  - If unavailable: **sodium benzoate** by continuous IV infusion. Start with a **loading dose** of 250 mg/kg over 2 hours (**max. 8g over 2h**) then 250-500mg/kg/24h (**max. 12g/24h**) (given via NG tube if no IV access).
  - Sample another ammonaemia before starting the scavenger drugs, without waiting for the results.

3 SEVERITY SIGNS = Consult / Transfer to Intensive Care

- **Coma** or **no neurological improvement** 3h after starting treatment.
- and/or **Severe hyperammonaemia (Infants >200 µmol/L - Children and adults >150 µmol/L):**
- and/or **Severe liver failure:** Prothrombin ratio < 30%, factor V < 50%
  - **Start sodium benzoate+sodium phenylacetate (Ammonul®)** 250mg/kg/day, ideally via central line, max. 12g (stop benzoate and phenylbutyrate).
  - Meanwhile, consider a complementary loading dose of sodium phenulbutyrate (Ammonaps®, Buphenyl®, Pheburane®): 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 infusion rate as above, NaCl 6 g/L (100mEq/L), potassium and calcium according to serum electrolytes + normal saline (NaCl 0.9%) on a Y-Set to administer a total of **1.5 L/m² of BSA/day** *(body surface area = (4 x Weight(kg)+ 7) / (Weight(kg) + 90)]*

4 MONITORING

- Follow-up tests (NH3, PT, electrolytes): at 4 hours if NH3>100 µmol/L (then reassess), at 6 or 12 hours if NH3<100 µmol/L depending on context (vomiting, fever)
- Capillary glucose q4h: target range 1-1.8g/L. If blood glucose > 2g/L with glycosuria, consider insulin 0.01 IU/kg/h with subsequent adjustment every hour. Consider reducing sugar intake (25 - 50%) if persistent hyperglycaemia despite insulin at 0.05 IU/kg/h and/or onset of hyperlactatemia > 3 mmol/L.

PATHOPHYSIOLOGY:

Carbonic anhydrase deficiency causes a secondary urea cycle disorder, exposing patients to a risk of endogenous intoxication by ammonia produced by the breakdown of aminoacids from proteins. It creates a risk of coma, particularly in the neonatal period, with lactic acidosis and hyperammonaemia.

The usual oral treatment can be (depending on the patient):

- None for some patients.
- Sodium benzoate and/or phenylbutyrate (Ammonaps®, Ravicti®, Pheburane®) and/or carglumic acid (Carbaglu®): 100-300mg/day divided tid or qid.
- Low-protein diet progressively broadenned with age.
- Whatever the baseline treatment, high-calorie and low-protein nutrition (or emergency infusion) during intercurrent infection.

CIRCUMSTANCES WITH 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 quickly. **They represent an emergency:** do the workup on the patient in A&E before admitting them 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:

- Acute neurological disorders (altered mental status, confusion, drowsiness, balance disorder, ataxia, behavioural change, 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 (Depakene®, etc.). Corticosteroids : consider the need if duration > 3 days. Use hydrocortisone if necessary in intensive care.

- All vaccinations are recommended (particularly influenza).

SURGERY under General Anaesthesia:

WARNING: never leave the patient fasting without an infusion. Implement the emergency protocol with infusion as described overleaf, in preparation for surgery.

ASSISTANCE WITH PRACTICAL ADMINISTRATION OF TREATMENTS:

- SODIUM BENZOATE IV: vial 1g = 10mL, dilute 1:1 by volume in 10% glucose in water. Contains 7 mEq of sodium per gram of benzoate.
- AMMONUL®: Recommended via central line. Use a 0.22µm filter. 50 mL bottle = 5g sodium benzoate + 5g sodium phenylacetate. Dilute in 10% glucose in water to obtain a concentration of 10 mg/mL. Contains 13.3 mEq of sodium per 10 mL of product. Available for emergency use.
- Carglumic acid (CARBAGLU®) 1 tablet = 200mg. Oral or via gastric tube (dilute in 10 mL of water).

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