HYPERAMMONAEMIA PROTOCOL (New patient)

1 DEFINITION AND SYMPTOMS

Hyperammonaemia is defined as elevated blood ammonia. Ammonia is a waste product of the protein metabolism, cleared by the liver via the urea cycle.

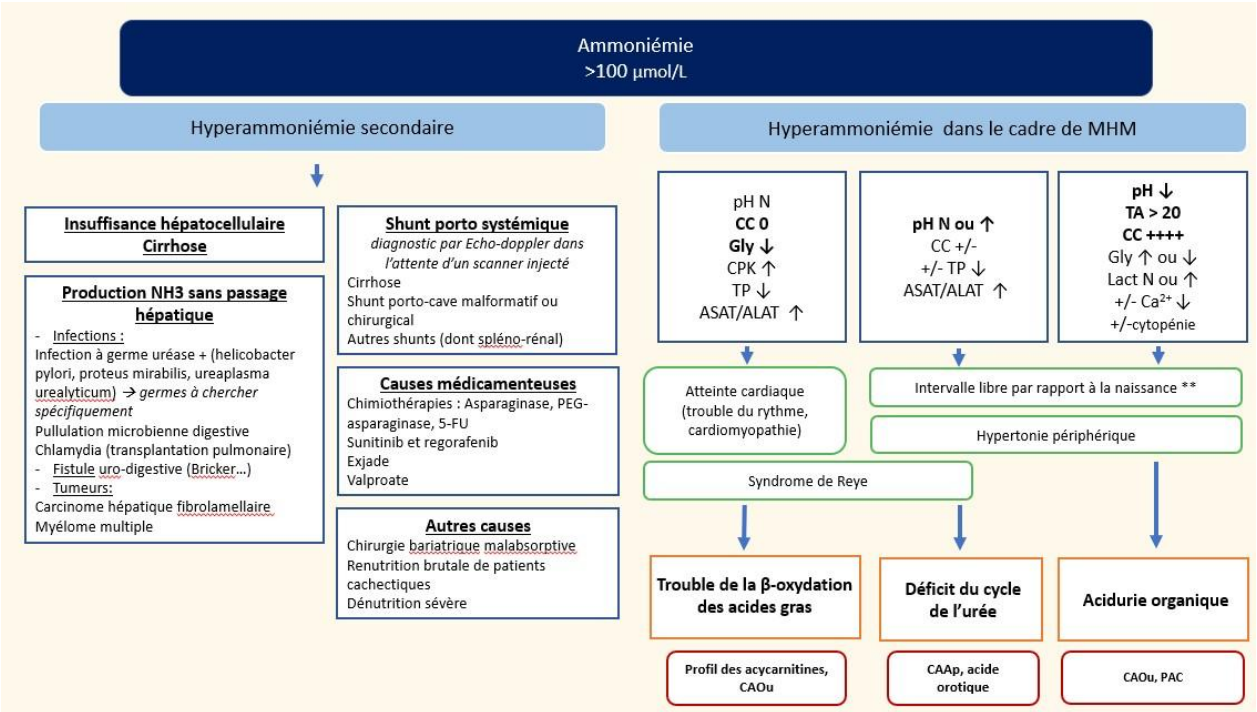
Ammonia is **toxic to the liver and the brain**. Therefore, treatment of hyperammonaemia is a **medical emergency.** Ammonia is an endogenous toxin. It should always be measured whenever an exogenous toxin assay is indicated, particularly when unexplained neuropsychiatric or hepatic/gastrointestinal symptoms are present.

The normal level of blood ammonia is <100 µmol/L in a neonate, and <50 µmol/L thereafter regardless of age. (conversion factor: mg/L x 58.7= µmol/L)

The level of ammonia in the blood reflects the total ammonia load and the distribution volume. Hence, the seriousness of hyperammonaemia at 100 µmol/L will vary depending on the patient's age (the risk being higher in older patients than in infants).

The causes of hyperammonaemia are linked to:

- A primary dysfunction of the urea cycle (urea cycle disorders: OTC, CPS, NAGS, citrullinaemia, arginosuccinic aciduria, arginase deficiency)
- A dysfunction of the urea cycle secondary to another inborn error of metabolism (IEM): fatty acid beta-oxidation disorder, organic aciduria, some defects of ketogenesis or ketolysis, some mitochondrial cytopathies.
- Secondary causes (see figure): hepatic failure, impaired clearance through the liver due to a portosystemic shunt *(increased serum bile acids)*, massive endogenous intoxication (infection with a urease-positive bacterium, gastrointestinal or urinary tract microbial overgrowth etc.), exogenous drugs affecting the urea cycle (chemotherapy, other treatments, etc.), tumour-related causes, etc.



Refer to the **Emergency section** on

2 EMERGENCY METABOLIC WORKUP

In all cases of hyperammonaemia in a previously unknown patient, the following tests should be performed, as a minimum, in order to eliminate an IEM:
blood gases, blood levels of lactate, glucose, ketones, electrolytes, urea, creatinine, CPK, complete liver function tests (AST, ALT, GGT, ALP, total and conjugated bilirubin)**, CBC-platelets, PT, factor V, fibrinogen.**
Specialist biochemical tests are also justified in this situation, including:

- plasma amino acid chromatography
- plasma acylcarnitine profiling
- urinary organic acid chromatography
- urinary orotic acid

It is important to take samples during the acute phase, and as soon as possible, ideally before starting any treatment (though this should not be delayed).

3 EMERGENCY TREATMENT TO BE IMPLEMENTED

Immediately check blood ammonia levels and start treatment without waiting for the results.

In an adult, if the initial diagnosis points to a secondary cause of hyperammonaemia (particularly hepatic encephalopathy related to cirrhosis or a shunt) refer to paragraph C.

A. Baseline infusion

- NO amino acids IV, no oral proteins: **stop feeding**
- **Infusion** of **10% glucose** (G10) with standard electrolyte additions* (not pure 10% glucose), 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)**

e.g.: Balanced electrolyte solution such as Bionolyte, B45, Glucidion etc. to which must be added 2 g/L NaCl to obtain 6 g/L in total or, if pre-made solutions not available, 10% glucose in water + 6 g/L NaCl and 2g/L KCl

- No lipids initially, **until fatty acid oxidation disorder has been excluded**. If indicated, 20% lipids given via a Y-set

Age	0 - 24 months	> 2 years	MAX. FLOW RATE
20% lipids (if needed)	0.4 ml/kg/h (2g/kg/day)	0.3ml/kg/h (1.5g/kg/day)	**20ml/h (500ml/24h)**

B. Ammonia clearance treatments: *Start sodium benzoate straight away and add other ammonia scavengers if available.*

- **Sodium benzoate** by continuous IV infusion Start with a **loading dose** of 250 mg/kg over 2 hours (**max. 8g over 2 hours**), then 250 to 500 mg/kg/24h (**max. 12g/24h**) (give orally or via NG tube if no venous access available). Take a sample for an ammonia assay at the end of the loading dose. [Sodium benzoate AP-HP 1 g-10 mL]; ampoule 1 g = 10 mL, to be diluted volume to volume in 10% glucose. Contains 7 mEq of sodium per gram of benzoate. Status = hospital preparation.
- Ammonaps orally only, possible as continuous administration via NG tube or in 4 to 6 doses: loading dose 250 mg/kg (max. 8g) then 250 to 500 mg/kg/24h (**Max. 12g/24h**). Combine with sodium benzoate.
- ***Carbaglu*** **Carbaglu®** (N-carbamyl-glutamate) if available: oral loading dose 50-100 mg/kg then maintenance dose 50 mg/kg/6h orally or via NG tube (Max. 8g over 24 hours).

C. Treatment of secondary causes

In addition to chelating treatment, start specific treatment for the secondary causes:

- Gastrointestinal microbial overgrowth: Tixtar (rifaximin) orally 500mg x2/day (adult) or 250 mgx2/day (child): in an adult only following advice from liver specialist
- Urinary microbial overgrowth: Flagyl (usual doses)
- Infection with a urease-positive bacterium: antibiotic treatment targeting intracellular bacteria
- 5-FU and PEG-asparaginase: consider a fruit and vegetable diet on a case-by-case basis, with the possibility of accompanying further treatment with chelator treatment.
- Seek liver specialist opinion for managing cirrhosis and/or shunt and/or liver failure
- Hepatic encephalopathy in an adult (while waiting for the advice of a liver specialist): Lactulose (gastric lavage or enema, then switch to oral administration following the dosage recommended by Vidal).

4 SIGNS OF SERIOUS ILLNESS/MANAGEMENT IN ICU

- Coma or no neurological improvement 3 hours after starting treatment
- and/or severe hyperammonaemia (Infant >200 µmol/L - Child & adult >150 µmol/L)
- and/or severe liver failure
  - Start Ammonul® (250 mg/kg/day), ideally via a central line, max.12g/24h (stop sodium benzoate and phenylbutyrate)
  - In the meantime, option of giving an additional loading dose of Ammonaps: 250mg/kg orally (max. 10g).
  - Consider haemodialysis
  - **Preferably use a central line as soon as possible to deliver a concentrated infusion** (risk of cerebral oedema) while maintaining glucose and sodium supply [example: 30% glucose (enough to provide the same glucose intake as above), NaCl 6 g/L (100meq/L), potassium and calcium according to serum electrolyte results + physiological saline (NaCl 0.9%) in parallel via a Y-set, to give a total intake of **1.5 L/m²/day** *(Body surface area = (4 x W + 7) / (W + 90))*
  - In ICU: Measures for neuroprotection and prevention of SBISO (Secondary Brain Insults of Systemic Origin)

5 MONITORING

- Follow-up checks (NH3, PT, serum electrolytes): at the end of the benzoate loading dose, then every 4 to 6 hours depending on progression. Correction of potential electrolyte abnormalities (in particular hypokalaemia in argininosuccinic aciduria)
- Capillary blood glucose every 4 hrs: target 1 to 1.8g/L. If blood glucose >2g/L and glycosuria, consider insulin 0.01IU/kg/hr, adjust in line with blood glucose checks.

Consider reducing sugar intake (25% to 50%) if, despite insulin therapy, hyperglycaemia persists at 0.05 IU/kg/h and/or appearance of hyperlactataemia > 3mmol/L.

NUMBERS AND MEDICAL SPECIALISTS

On-call telephone numbers for metabolic emergencies:

At night, only 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. 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