Emergency Management of Hyperammonaemia in The Newborn

HYPERAMMONAEMIA IS A TIME CRITICAL MEDICAL EMERGENCY

1. Introduction

Hyperammonaemia is a pathological build-up of ammonia in the body, usually caused by an inborn error of metabolism (IEM) or severe illness (see section 6). Ammonia is produced by breakdown of amino acids(protein) and is toxic to the brain if raised. It can cause irreversible damage depending on the degree and duration of the ammonia peak. Hyperammonaemia is therefore **a medical emergency,** and action is needed to reduce levels quickly. This guideline is based on the British Inherited Metabolic Disease Group guideline on Undiagnosed Hyperammonaemia Diagnosis and Immediate Management. (https://bimdg.org.uk/wp-content/uploads/2024/12/Hyperammonaemiaand_manage_2016_415469_09092016.pdf)

2. Interpretation of Ammonia.

- Normal Values should be < 50 µmol/l, but mildly raised levels up to 80 µmol/l are common.
- Any value >100 µmol/l requires urgent attention and a repeat sample sent.
- **Free Flowing samples (venous or arterial should be sent urgently on ice to the laboratory with in 20 minutes of sampling. Capillary samples and POD system should not be used.**
- If ice is not readily available, transport the sample as quickly as possible at room temperature. Even if delayed the sample should still be analysed and the result fed back urgently, with a comment from the laboratory on the possibility of an artefactual rise in ammonia, caused by the delay. If the result is >100micromol/l a repeat sample should be sent as soon as possible and without delay.
- The risks posed by not analysing a screening sample for hyperammonaemia because of poor transport conditions is outweighed by delay in recognition of possible hyperammonaemia secondary to sample rejection
- Artificially raised values may occur if:
    - Haemolysed sample
    - Delay in analysis
    - Excess muscle activity such as status epilepticus.

- Ammonia Levels up to 180 µmol/l can be seen in newborn babies with significant illness.
- If Ammonia levels remain < 100 mmol/l but >80mmol, it should be repeated non urgently (in 4-6 hrs), and baby should not be discharged until is decreasing trend of ammonia levels < 80 mmol is noted.
- **Hyperammonaemia is considered significant when the values are > 200 µmol/l and needs urgent escalation and intervention as an inherited disorder is very likely**.
- Patients with an ammonia >400 µmol/l resistant to pharmacological treatment must start renal replacement therapy in form of haemofiltration/haemodialysis within 6 hours of identification.

3. Management (See section 3.6 for Flow Chart)

3.1Principles of acute management

a) Supportive treatment: ABC (Airway, Breathing, Circulation), maintain glucose homeostasis, manage seizures
b) Reverse Catabolism: Stop feeds and IV protein, treat any hypoglycaemia, and start intravenous hydration.
c) Ammonia excretion: Use scavenger medications or hemofiltration-haemodialysis
d) Treat underlying condition.
e) Neuroprotection: Neuromonitoring and supportive management

3.2Any ammonia level ≥ 100µmol/l:

a) Repeat the sample urgently and Contact the Consultant Neonatologist
b) Stop enteral feeds immediately
c) Support airway and breathing and have a low threshold for mechanical ventilation.
d) Send hypoglycaemia screen if based on age and treat with 2.5 ml/kg of 10% glucose bolus intravenously.
e) Start IV fluids of 10% Glucose at an appropriate maintenance rate till discussion with metabolic team. Aim for blood glucose of 6-10 mmol to reduce risk of catabolism. Consider if the baby requires additional fluids for dehydration.

f) Give 10 ml/kg bolus of 0.9% Sodium Chloride routinely, 20ml/kg if baby has shock, repeat bolus if poor perfusion persists.
g) If hyperglycaemia > 14 mmol, start insulin infusion (as per local policy), rather than reducing glucose infusion rate.
h) Take blood culture samples and start Antibiotics (as per local policy) for presumed sepsis.
i) See section 4 for other investigations
j) See section 5 for key elements of history to ask
k) Examine and document any signs of illness including encephalopathy

3.3 Monitoring

- Monitor ammonia levels, glucose and blood gases 1-2 hourly until ammonia is decreasing.
- Ammonia toxicity is worsened by hypoxia and hypotension, hyperthermia, and hypoglycaemia. Maintain pH, pO2, and pCO2, glucose, temperature, and blood pressure in the normal range.
- Monitor electrolytes, renal and liver function 6 hourly or more frequently as clinical situation indicates. There is a serious risk of hypokalaemia so monitor potassium levels and supplement where required.
- Watch continuously for signs of rising intracranial pressure, such as increasing irritability, increasing hypertension and bradycardia.

3.4 Additional Actions for any ammonia levels > 200 µmol/l

- Inform neonatal consultant, who will contact on call metabolic consultant urgently.
- Repeat Ammonia sample urgently.
- Treatment of Hyperammonaemia with ammonia scavengers, will be advised by metabolic consultant. (depends on ammonia level and clinical status, such of presence of encephalopathy)
- If scavenger treatment is advised by metabolic consultant, this should be commenced within 30 minutes of decision to treat.
- Scavenger infusions can be given peripherally. Infusions are compatible with glucose and electrolyte containing maintenance fluids.
- Once treatment is started:
    - Repeat ammonia one hour after infusions have started
    - Insert a second peripheral cannula

- Intubate and ventilate to reduce metabolic demand and ammonia production
- Commence aEEG and NIRS monitoring and perform head USS
- Insert arterial line
- Consultant to discuss potential transfer with PICU consultant

- Indications for CRRT (Continuous renal replacement therapy):
    - Ammonia > 400µmol/l (CRRT should be started within 6 hours of identification)
    - Development of an encephalopathy

3.5 Ammonia scavengers

Use only under guidance of metabolic team. Refer to monographs and BIMDG infusion calculator – Link below
In an emergency the loading dose should be given initially followed by maintence dose.

Drug	Loading dose (Over 90 Mins)	Maintenance (Over 24 Hours)	Maximum Total Dose (In 24 Hours)	Sodium Content of Maintenance Dose
Sodium Benzoate	250mg/kg	250mg/kg	500mg/kg	3.5mmol/kg/d
Sodium Phenylbutyrate	250mg/kg	250mg/kg	600mg/kg	2.8mmol/kg/d
Arginine	150mg/kg	300mg/kg	500mg/kg	Nil
Carnitine	100mg/kg	100mg/kg	300mg/kg	Nil
	Should NOT be given if evidence of cardiomyopathy, and any arrhythmia or VLCFA Oxidation disorder suspected			
Carglumic acid	250mg/kg stat dose enterally Consider if suspect NAGs deficiency or organic acidaemia			
Hyperlink for infusion Calculator	https://bimdg.org.uk/wp-content/uploads/2024/12/UCDcalculator_for_UNDIAGNOSED_v6-1-289867-04-12-2013_288879_16042017.xls			

3.6 Flowchart for emergency management of hyperammonaemia (Ammonia > 100µmol/l)

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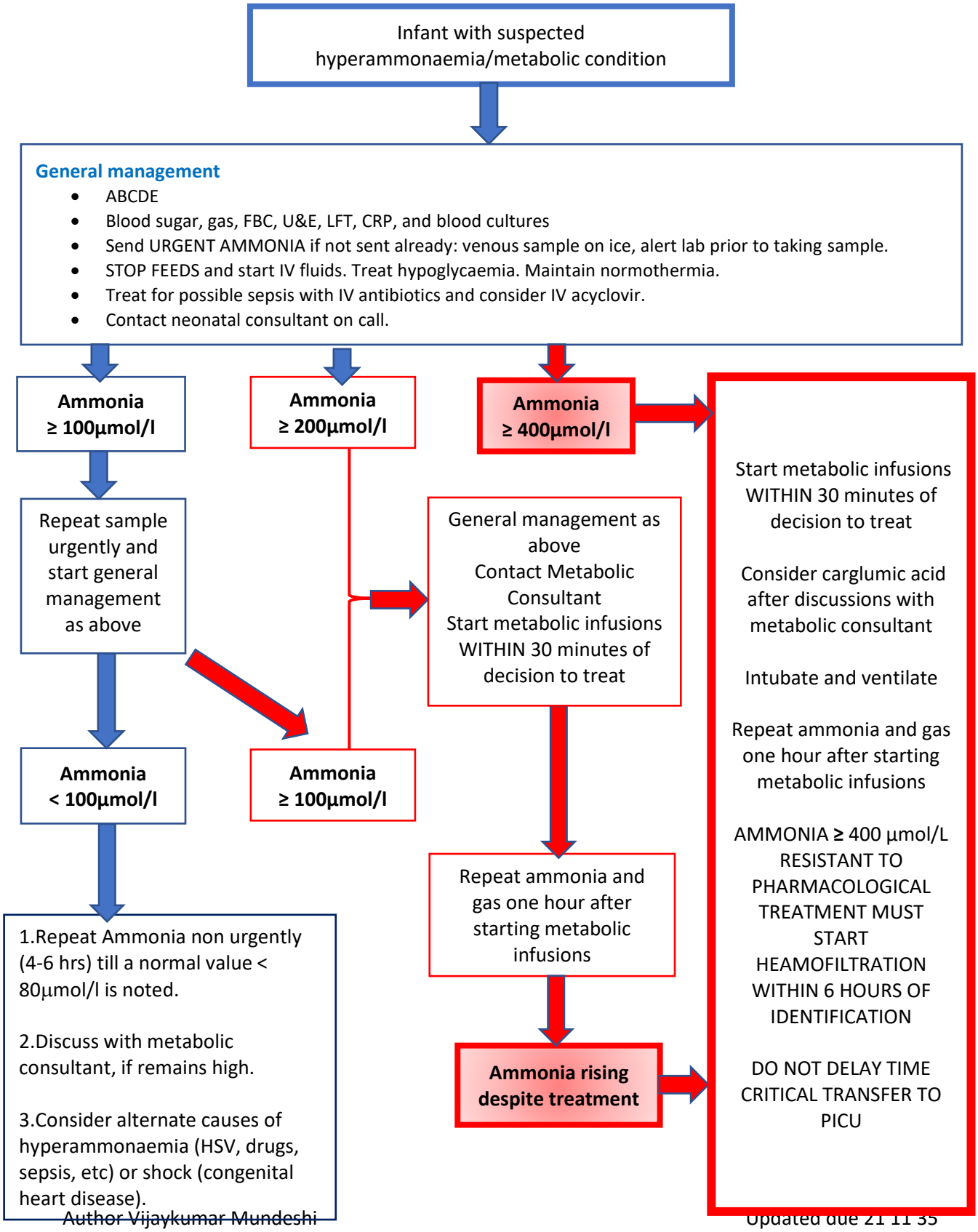
THE RISK OF PERMANENT NEUROLOGICAL DAMAGE AND DEATH IS DIRECTLY RELATED TO THE DEGREE AND DURATION OF AMMONIA PEAK



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4. Additional Investigations

- Plasma urea, creatine & electrolytes, liver function tests, clotting studies
- Hypoglycaemia 'screen' if blood glucose < 2.6 mmol/l
- Plasma amino acids*
- Blood spot for acyl carnitine profile*
- Blood gas and Lactate
- Sepsis screen: CRP / FBC / Blood culture/ Urine Culture/CSF (if stable)
- Urine for ketones, amino and organic acids including orotic acid*
- EDTA and clotted samples to store
- Genetics samples.

***As soon as possible after presentation (Prioritise these)**

5. History and Presentation

Timing of presentation depends on the underlying cause and, in IEM, usually occurs once feeds are introduced.

- Tachypnoea
- Lethargy
- Poor feeding, persistent vomiting.
- Temperature instability
- Encephalopathy, seizures, and coma
- Bleeding and coagulopathy
- Acidosis, alkalosis, high lactate, electrolytes imbalance and hypoglycaemia.

Ensure the following history is taken:

- Antenatally concerns of a metabolic condition.
- Family history of metabolic condition.
- Parental consanguinity.
- Sibling deaths without apparent cause

6. Causes of hyperammonaemia

Inherited disorders	Acquired conditions
<u>Urea cycle enzyme defects</u> • Carbamoyl phosphate synthetase deficiency • Ornithine carbamoyl transferase deficiency • Arginosuccinate synthetase deficiency (Citrullinemia, ASS def) • Arginosuccinate lyase deficiency (Arginosuccinic aciduria, ASA or ASL def) • Arginase deficiency • N-acetyl glutamate synthetase deficiency <u>Transport defects of urea cycle intermediates</u> • Lysinuric protein intolerance (LPI) • Hyperammonaemia-hyperornithinaemia-homocitrullinuria syndrome (HHH syndrome) • Citrin deficiency (citrullinemia type II) <u>Organic acidurias</u> • Propionic acidaemia • Methylmalonic acidaemia • Isovaleric acidaemia Other metabolic disorders may cause mild- moderate hyperammonaemia: • Fatty acid oxidation disorders, congenital lactic acidosis (including pyruvate carboxylase deficiency) and hyperinsulinism-hyperammonaemia	• Transient hyperammonaemia of the newborn • 'Reyes' syndrome • Liver failure from any cause, both acute and chronic • Valproate therapy • Infection with urease positive bacteria (particularly associated with stasis in the urinary tract) • Systemic herpes simplex infection • Gastrointestinal haemorrhage

References and Links

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3. https://northwestchildrensodnhub.nhs.uk/wp-content/uploads/2025/01/Hyperammonamia-Guideline-ver-3-FINAL-28th-Jan-2025.pdf

4. https://metbio.net/wp-content/uploads/MetBio-Guideline-PERE918546-10-12-2018.pdf

5. Ni B, Qin M, Zhao J, Guo Q. A glance at transient hyperammonaemia of the newborn: Pathophysiology, diagnosis, and treatment: A review. Medicine (Baltimore). 2022 Dec 2;101(48): e31796. doi: 10.1097/MD.0000000000031796. PMID: 36482558; PMCID: PMC9726343.

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