Neonatal and Paediatric Hyperammonaemia Guideline

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The Yorkshire and Humber
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Aims

The aim of this clinical guideline is to help health professionals to make informed decisions about the diagnosis and management of neonatal and paediatric hyperammonemia.

Objectives

To provide evidence-based recommendations for appropriate diagnosis and investigation of hyperammonemia

To provide structured pathway for stabilization, timely escalation and transfer for patients needing critical care for severe hyperammonemia

Disclaimer

This clinical guideline is based on available evidence in conjunction with clinical expertise and experience and represents the views of the Yorkshire and Humber Paediatric Critical Care Network and Embrace Transport Service. The current guideline is not intended to take the place of clinicians' judgment and does not override the individual responsibility of healthcare professionals to make their own treatment decisions about care on a case-by-case basis using their clinical judgment, knowledge and expertise along with patient/family wishes.

Users always are urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within this guideline.

Clinical advice is always available from Embrace and the PICU teams on a case by case basis. Please feel free to contact Embrace (01142688180) for any further support and advice.

Guideline Outline

Clinical suspicion of a metabolic disorder/hyperammonemia

- A to E
- Blood sugar, gas, FBC, U&E, LFT, CRP, and cultures
- Send URGENT AMMONIA: venous sample, on ice, alert lab prior to taking sample to prevent processing delays
- Treat for possible sepsis with broad spectrum IV antibiotics and IV acyclovir if concerns about herpes infection
- STOP FEEDS and start IV fluids containing 10% dextrose

Ammonia ≥ 150 µmol/L

Repeat ammonia. Call lab to ensure no delays in processing sample.

Ammonia < 200

Discuss with on call metabolic consultant & inform Embrace if clinically deteriorating. Consider alternate causes of hyperammonaemia (HSV, drugs, sepsis, etc) or shock (congenital heart disease in a neonate)

Ammonia ≥ 200

Ammonia ≥ 200 µmol/L

- Contact Metabolic Consultant
- Start metabolic infusions **WITHIN 30 minutes** of decision to treat (pg 3)
- 2nd peripheral venous access

Repeat ammonia and gas one hour after starting metabolic infusions

Ammonia rising despite treatment

Ammonia ≥ 400 µmol/L

HYPERAMMONAEMIA IS A TIME CRITICAL MEDICAL EMERGENCY

AMMONIA >400 µmol/L RESISTANT TO PHARMACOLOGICAL TREATMENT MUST START HEAMOFILTRATION WITHIN 6 HOURS OF IDENTIFICATION

- Start metabolic infusions **WITHIN 30 minutes** of decision to treat (see pg 3)
- Contact anaesthetic SpR/Cons for assessment
- Intubate and ventilate after discussions with PICU consultant via Embrace
- Consider carglumic acid after discussions with metabolic consultant
- Send repeat ammonia pre-transfer

DO NOT DELAY TIME CRITICAL TRANSFER TO PICU!

Embrace: 0114 268 8180Metabolic consultant on call (at Royal Manchester Children's Hospital): 01612761234

TIME IS BRAIN WHEN MANAGING HYPERAMMONAEMIA. AMMONIA IS NEUROTOXIC AND THE RISK OF PERMANENT NEUROLOGICAL DAMAGE AND DEATH IS DIRECTLY RELATED TO THE **DEGREE** AND **DURATION** OF AMMONIA PEAK. TREAT THIS WITH THE UTMOST URGENCY.

Reference: NWTS Guideline for the Management of Neonatal and Paediatric Hyperammonaemia. 2018.

Introduction

Hyperammonaemia is a **TIME CRITICAL medical emergency** with the risk of death and serious neurological damage.

It is most commonly associated with inherited disorders of amino acid and organic acid metabolism. However, it can also be seen in liver failure, sepsis, systemic herpes simplex in neonates, and drugs (sodium valproate, carbamazepine, leukaemia treatment with asparagine etc.) [1]

Ammonia is neurotoxic where degree (peak ammonia level) and duration of hyperammonaemia is directly related to poor neurological outcomes. Good outcomes are seen when the ammonia remains <250 µmol/l [1]. Significant neurological deficit is associated when ammonia rises above 350 µmol/l [1,2]), with levels above 1000 µmol/L indicating a very high risk of death or neurological damage. [1,3]

Therefore, patients with an ammonia **>400 µmol/l** resistant to pharmacological treatment must start renal replacement therapy in form of **heamofiltration/haemodialysis within 6 hours** of identification [4]. Adequate resuscitation, timely stabilisation and appropriate escalation to invasive ventilation and haemodynamic support goes hand in hand with the targeted metabolic management and is the key to good outcome. Maximal drug therapy should be continued until ammonia is reduced by filtration and any alteration should be done in conjunction with the metabolic team. Meticulous attention to hydration, neuro-protection, stopping catabolism & promoting anabolism, glucose and electrolyte management is vital for hyperammonemia management.

Presentation

Hyperammonaemia can present in a wide range of non-specific symptoms, making diagnosis challenging. Most children present in the neonatal period with vomiting, irritability or somnolence, poor feeding, failure to thrive, poor tone and developmental delay. Acutely these neonates can present in shock, with seizures, temperature instability, jaundice, hepatomegaly, low blood sugar, raised lactate, respiratory alkalosis (organic acidemia) and/or metabolic acidosis/alkalosis (urea cycle disorders). [4]

Toddlers present more often with gastrointestinal symptoms such as vomiting and poor feeding. Whereas older children and adolescents present with more neurological symptoms such as altered behaviour, signs of intoxication, lethargy and encephalopathy.

Less commonly, metabolic conditions affecting fatty-acid oxidation can also present with cardiomyopathy and pulmonary haemorrhages.

A family history of consanguineous parents, previous miscarriages, previous unexplained neonatal deaths, maternal HELLP or acute fatty liver in pregnancy, or increased in-utero foetal movements (seizures) should raise suspicion of inborn errors of metabolism.

Diagnosis

1. **URGENT AMMONIA.** *Venous free flowing* sample taken and sent *on ice* and walked quickly to the lab. The lab should be forewarned that a sample is to be expected, allowing for an expedited result. Heal pricks, squeezed samples, samples at room temperature, and delays in processing will give a falsely raised result. Results should be available within 20 minutes. Healthcare professionals should be aware of the local ammonia analytical method used in their lab focusing on whether it is a quantitative analysis or point of care test. Some DGH laboratories use ammonia checker as point of care/screening test using reflectance meters. The working range of this analysis is between 8-285

µmol/l making it unsuitable for diagnosis and follow-up of clinically significant hyperammonemia and an urgent quantitative ammonia measurement should be sent for accurate levels to help clinical decision making. Please liaise with the nearest metabolic lab (Leeds or Sheffield) to forewarn them to expect the sample avoiding delay in analysis and streamline communications.

2. If ammonia >150 µmol/L, repeat sample (Sample should be sent for quantitative analysis immediately if using reflectance meters/ammonia checker/point of care test and treatment should be started immediately without waiting for the results)
3. If ammonia **>200 µmol/L, START TREATMENT** and repeat sample
4. **Second IV access:** FBC, U&E, LFT, bone profile, clotting, lactate, glucose, CRP, acylcarnitines, plasma amino acids, blood gas, blood ketones and blood cultures. Efforts should be made to collect the first urine sample passed following presentation for reducing substances, ketones and organic acids including orotic acid (Catheterize if necessary to obtain sample). Ensure samples for acyl carnitines and amino acid analysis are sent in timely fashion – not only will this help to reach a diagnosis quicker in order to tailor treatment but also some diagnoses/interpretation can be more difficult to make once the patient is anabolic.

Initial Management

1. **Stop feeds**. This reduces further protein load.
2. **Treat Hypoglycemia: 2 ml/kg of 10% glucose bolus** (equivalent of 200 mg/kg). Glucose will stimulate insulin release and turn off catabolism.
3. **10 mL/kg fluid bolus (usually 0.9% saline however choice of fluid can be crystalloid or colloid based on local policies)**: If peripheral circulation is poor or child clinically shocked, further resuscitation with volume and/or inotropic support is needed with close monitoring of heart rate, blood pressure and perfusion till shock is resolved or haemodynamic parameters improve.
4. **Maintenance fluids**: 10% glucose + 0.9% saline. **Rate**: Calculate maintenance as you would for any child; give 1/3 of the total for 24 hours over the first 6 hours and then the remainder in 18 hours. [5]. There is a serious risk of hypokalaemia so add in potassium as early as safely possible. Refer to BIMDG website for detailed instructions if needed: ***http://www.bimdg.org.uk/store/guidelines/intravenous_fluidsrev4_864191_09092016.pdf***
5. **Start broad spectrum IV antibiotics.** Consider IV acyclovir if concerns about herpes infection. Both bacterial and HSV sepsis can cause hyperammonaemia.
6. **Check blood sugar hourly.** Aim blood sugar 6 - 10 mmol/L. If plasma glucose rises above 14 mmol/L and there is glycosuria start IV insulin infusion (0.025 units/kg/hr-titrated to blood glucose levels) instead of reducing glucose intake. However, if there is a lactic acidosis discuss with a metabolic consultant prior to starting insulin.
7. **Contact on call metabolic consultant for further advice and guidance:**
   Royal Manchester Children's Hospital: 0161 276 1234.

Metabolic Drugs

Start metabolic infusions upon the guidance of the metabolic consultant within 30 minutes of decision to treat. Delays are unacceptable and every effort should be made to source and start the metabolic drugs as soon as possible. Clinicians should be aware of their local arrangements regarding metabolic drugs (different arrangements throughout the region: Some DGHs store their own metabolic boxes while other

may rely on local PICU to taxi the metabolic box). Metabolic boxes are available in Sheffield and Leeds PICU and further support is available from on-call pharmacists if needed.

Infusions can be administered **peripherally**. Infusions are **compatible with each other on the same line** and with glucose and electrolyte-containing maintenance fluids.

Table 1. Metabolic Infusions for Children < 10 kg

	Loading Dose	Maintenance Dose	Preparation
Sodium Benzoate	250mg/kg over 90minutes = 5ml/kg over 90minutes	250mg/kg/day by continuous infusion = 0.2ml/kg/hr	Use the 1g in 5ml preparation. Dilute 2.5g (12.5ml) to 50ml with 10% glucose.
Sodium Phenylbutyrate	250mg/kg over 90minutes = 5ml/kg over 90minutes	250mg/kg/day by continuous infusion = 0.2ml/kg/hr	Use the 1g in 5ml preparation. Dilute 2.5g (12.5ml) to 50ml with 10% glucose
L-Arginine	150 mg/kg over 90 minutes = 3mL/kg over 90 minutes	150-300mg/kg/day by continuous infusion = 0.12-0.26ml/kg/hr	Add 25ml arginine 10% pre-mixed solution to 25ml 10% dextrose to make 50mg/ml solution which is maximum concentration peripherally
Carglumic Acid Provided by Embrace	250mg/kg as a single ENTERAL dose		Mix 200 mg tablet in 2.5mL of water to give 80 mg/mL. Shake gently. Draw up appropriate volume and administer immediately down NGT. Flush NGT with additional water to clear.
L-Carnitine *		25mg/kg FOUR times a day.	Can be given undiluted as an IV injection over 2-3 minutes.

*~L-Carnitine should not be used if LCFA disorder is suspected — always discuss with Metabolic consultant first

Table 2. Metabolic Infusions for Children >10 kg

	Preparation	Loading Dose	Maintenance Dose
Sodium Benzoate & Phenylbutyrate	Add 12.5g of sodium benzoate AND 12.5g of sodium phenylbutyrate to a SINGLE 500ml bag of 10% glucose.	250mg/kg (10mL/kg) over 90 minutes = run bag at 6.67ml/kg/hr for first 90 minutes	0.42ml/kg/hr
L-Arginine	As per children < 10 kg		

The following tables and calculations are courtesy of the **BIMDG** and **North West & North Wales Transport Service** paediatric and neonatal hyperammonaemia guidelines. Please refer to the BIMDG website if more detail is required at www.bimdg.org.uk

Pre-Transfer

- If the hyperammonaemia is resistant to infusions and/or the child is haemodynamically unstable contact Embrace if at a DGH or PICU if at Leeds/Sheffield Children's Hospital.
- **Contact on-call anaesthetist SpR/Consultant.** Most patients will require intubation and ventilation.
- **Indications for intubation**: apnoea, circulatory failure, reduced GCS, intractable seizures, hemofiltration and central line insertion. Ammonia toxicity is worsened by hypoxia and hypotension, hyperthermia and hypoglycemia. Thus target normal pH, pO_2, and pCO_2 and age appropriate other neuroprotective measures. [1]
- **Repeat ammonia immediately before transfer**. This result will determine whether haemofiltration is needed on arrival to PICU.
- It must be a **Time Critical Transfer.**
- If Embrace are unavailable the local hospital is responsible for urgent time critical transfer with YAS to PICU.

On PICU

- **Urgent renal replacement therapy (CVVHD/HD) is needed for treatment** for hyperammonaemia and must be started **within 6 hours** of identification. Ammonia crosses the dialysis membrane quickly. The higher the flow rate, the more effective the clearance. [1, 6]
- **CVVH/HD indications** include: Ammonia >400 µmol/l resistant to pharmacological treatment, Maple syrup urine disease (raised plasma leucine), lower threshold for neonatal presentation (ie, on day 1-2 of life) or significant encephalopathy. Always discuss with PICU consultant. [1, 9]
- Have a lower threshold for starting haemofiltration in patients with organic acidaemia. [10]
- The most experienced/senior clinician must insert the biggest Vascath possible, preferably in the internal jugular to prevent recirculation. Following one failed attempt, it is imperative to arrange surgical line by contacting on call paediatric surgery team or seek help from interventional radiology. The PICU consultant will decide on further attempts if delay in help from surgeons or interventional radiology is expected.
- **Consider renal input if patient suitable for haemodialysis (Weight>8Kg, haemodynamically stable and renal team can facilitate HD session).** Although haemodialysis will drop the ammonia levels quickly it might be poorly tolerated in smaller and sick children and haemofiltration (CVVH) will be the only viable option in these unstable patients. HD associated hypotension and fluid shifts may offset the benefits of quick decrease in ammonia levels
- **High volume haemofiltartion** could be employed as an alternative if ammonia levels >1000 and patients is haemodynamically stable to tolerate the high flows.
- **Discussion with ECMO team for suitable patients like severe cardiac dysfunction or haemodynamically unstable patients as a stabilising measure and facilitate renal replacement therapy via the ECMO circuit.**
- Liaise with neurosurgeons & consider ICP monitoring for patients with clinical signs of raised ICP. [9]
- Most patients will have a slight rebound increase in ammonia following CVVHD. This can be avoided by tailing off CVVHD rather than stopping abruptly. This usually does not require repeat CVVHD. [1]

It is thought this is secondary to rapid clearance of the ammonia from the circulation, followed by a slower movement out of the tissues.

- Peritoneal dialysis can be considered in very small infants if CVVHD not possible/tolerated, however this is far less effective. [7,8]
- It is important to re-introduce enteral feeds containing protein within 48 hours in order to prevent protein catabolism and worsen decompensation. [9] Giving adequate calories is important and giving IV lipid should be considered at an early stage- liaise with metabolic consultant and dieticians.
- On-going liaison with the metabolic team for further investigations, family update and changing treatment according to the most possible diagnosis.

Resources

1. University Hospital Leicester Hyperammonaemia Guideline 2016
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10. Haberle et al. Suggested guideliens for the diagnosis and management of urea cycle disorders. Orphanet Journal of Rare Diseases 2012; 7:32

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