Management of neonates and children with hyperammonaemia and inborn errors of

For more detailed information, please read the complete guideline

Initial investigations*:
- Blood glucose
- Blood gas & Anion Gap
- Ammonia
- Ketones (blood and urine)
- Lactate
- Plasma Urea & creatinine, electrolytes
- Liver function tests & Clotting screening
- Creatine Kinase, Calcium

*(*Ensure samples taken prior to treatment)*

Red flags for suspicion of a metabolic condition:
- Poor feeding and lethargy
- Acute progressive encephalopathy +/- seizures
- Initial well period and progressive deterioration
- Absence of sepsis risk factors or history of perinatal insult
- Consanguineous parents +/- family history
- Deterioration despite normal supportive therapy
- Biochemical clues

Repeat ammonia immediately if >100 mmol/l in children, >150 mmol/l in neonates (to recheck always rapidly if elevated)

Is this a TIME-CRITICAL TRANSFER?
Hyperammonaemia needs URGENT discussion with Metabolic team and PaNDR

Refer early to PaNDR for advice (01223 274 274)

Differential diagnosis of collapsed neonate:
- Neonatal septicaemia
- Perinatal insult (i.e.HIE)
- Ductal dependant congenital heart disease (CoAo. HLHS)
- Liver failure
- Liver shunt (persistent Arantius canal, portal hypertension, arterio-venous malformation)

Initial management & Stabilisation
- Support A-B-C-D
  - If profound encephalopathy, intractable seizures, or recurrent apnoeas, intubate
  - If signs of acute circulatory failure, start fluid resuscitation (up to 40-60 ml/kg)
  - If signs of refractory circulatory failure, consider start peripheral inotropic support (adrenaline or dopamine)
  - If seizures, treat as per APLS
- Correct acidosis if present
- Stop any source of protein intake (feeds or TPN)
  - NGT or OGT and keep the patient NBM
  - peripheral dextrose infusion with electrolytes (0.45% sodium Chloride)
- Drive Anabolism
  - If hypoglycaemia, give dextrose 10% 2.5 ml/kg as an IV bolus
  - Start dextrose infusion (10% dextrose) at a rate to provide 8-9 mg/kg/min
  - If hyperglycaemia > 10 mmol/l +/- glycosuria, start an insulin infusion rather than reducing the glucose intake.
- If signs of infection, start ATB as per local policy (consider adding Acyclovir)
- Remove toxin substance (ammonia)
  - Start IV ammonia scavengers always after discussion with the Metabolic team
  - In an emergency the loading dose should be given initially followed by the maintenance dose (see table below)

Drug	**Loading dose over 90 minutes**	**Maintenance dose (over 24 hours)**	**Max daily dose (every 24h)**
Sodium Benzoate	250 mg/kg	250 mg/kg/24h	500 mg/kg
Sodium phenylbutyrate	250 mg/kg	250 mg/kg/24h	600 mg/kg
Arginine	150 mg/kg	300 mg/kg/24h	500 mg/kg
Carnitine**	100 mg/kg	100 mg/kg/24h	300 mg/kg

Carnitine should NOT be given if there is evidence of a cardiomyopathy, any cardiac arrhythmia or if a long chain fatty acid oxidation disorder is suspected

References:
1) Rice, G. M.; Steiner, R. D. (2016). Inborn Errors of Metabolism (Metabolic Disorders). Pediatrics in Review, 37(1), 3–17. doi:10.1542/pir.2014-0122
2) Jeanmonod R, Asuka E, Jeanmonod D. Inborn Errors Of Metabolism. [Updated 2021 Nov 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459183/
3) British Inherited Metabolic Disease Group website and guidelines. https://bimdg.org.uk/store/guidelines/HyperammonaemiaAnd_manage_2016_415469_09092016.pdf

Management of neonates and children with acute hyperammonaemia and other Inborn errors of metabolism

1 Scope

For use within Paediatric and Neonatal Decision Support and Retrieval Service (PaNDR) for the East of England.

2 Purpose

To provide guidance on the management of infants and children presenting with acute new onset hyperammonaemia and a suspected Inborn error of metabolism.

3 Definitions

IEM	Inborn errors of metabolism
MSUD	Maple Syrup Urine Disease
EBS	Emergency Bed Service
PAA	Plasma amino acids
APLS	Advanced Paediatric Life Support
ICP	Intracranial Pressure
FAO	Fatty Acid Oxidation

4 Introduction

Inborn errors of metabolism (IEM) are a heterogeneous group of disorders that may be inherited or may occur as the result of spontaneous de novo mutation. These diseases are caused by deficiencies of the metabolic pathways involved in either the breakdown or storage of carbohydrates, fatty acids, and proteins (*see table 1 in appendix*). Most are inherited as autosomal recessive. Rarely, they are autosomal dominant and X-linked. Some of these disorders can be detected in newborn screening (NBS) programs. In fact, with the addition of tandem mass spectrometry (which includes acylcarnitine profile and amino acid analysis), more than 40 disorders of intermediate metabolism can now be detected. Because many of these conditions are treatable, their early detection and diagnosis can be lifesaving.

The disorder may cause complete dysfunction of the involved enzyme, or it may be partial or incomplete. This reflects the different clinical presentation of some of these defects in relation to its severity and time of onset. Conditions with severe or

complete dysfunction of the involved enzyme will present early in life (i.e. neonatal period) and could lead to catastrophic consequences if left untreated.

Those already known metabolic disorders should be discussed with the duty metabolic consultant. If a new metabolic condition is suspected, early discussion with the metabolic on-call team is advisable, especially for hyperammonaemia. For the EoE, the 2 metabolic base centers are Great Ormond Street and Evelina Children's Hospital.

Should and urgent discussion is required, EBS will facilitate a conference call between the referring center, the PaNDR consultant and the duty metabolic consultant.

5 Clinical presentation

Clinical presentations may vary depending upon degree and type of enzyme involvement, with neurologic and gastrointestinal manifestations as the 2 most common presentations.

- Encephalopathy, seizures, apnoea
- Hypotonia and lethargy
- History of poor feeding and hypoglycaemia
- Vomiting
- Hypocapnia and tachypnoea
- Signs of cardiac failure / cardiomyopathy
- Hepatomegaly, Liver dysfunction
- Dysmorphism
- Family history: consanguineous parents, family history of metabolic condition, miscarriages

Red flags for suspicion of a metabolic condition:

- Initial well period and progressive deterioration
- Absence of sepsis risk factors or history of perinatal insult
- Consanguineous parents +/- family history
- Deterioration despite normal supportive therapy (fluids, antibiotics, etc)
- Biochemical clues

6 Differential diagnoses for an acute unwell neonate

- Neonatal septicaemia
- Perinatal insult (i.e. hypoxic-ischemic encephalopathy)

- Congenital heart defects – Ductal dependant circulation as duct closes, child will look progressively unwell (i.e. CoAo, HLHS)

7 Screening tests for IEM

The following tests are mandatory to complete for any acute unwell neonate with suspected inborn error of metabolism. These tests will compliment other important investigations for an acute unwell neonate (i.e ECG & Echocardiogram, brain CT scan or Cranial USS, lumbar puncture, and blood cultures)

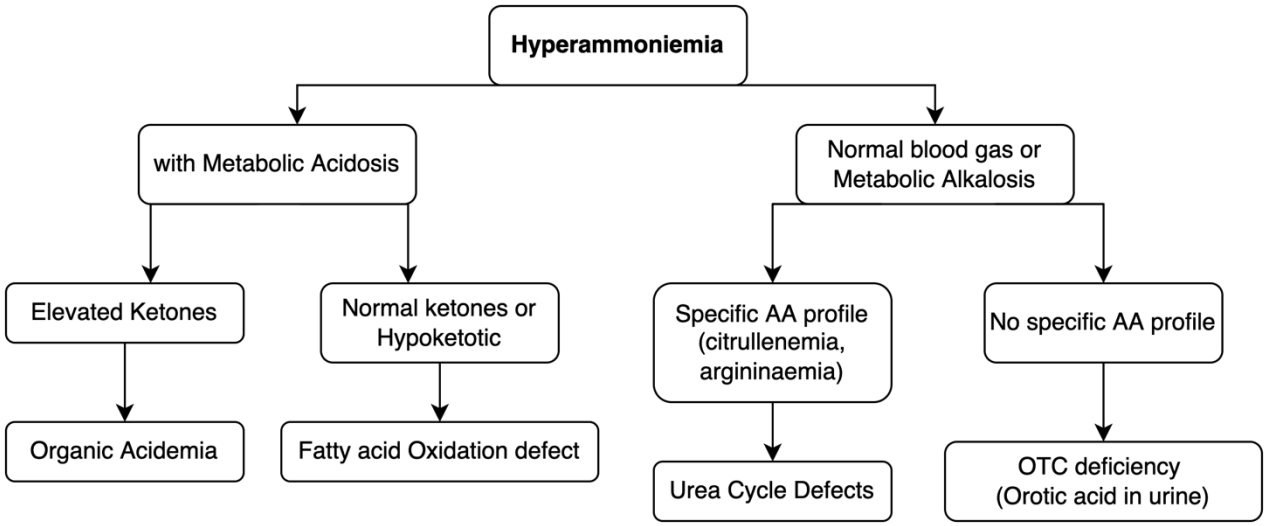
Blood glucose	Hypoketotic hypoglycaemia (HKHG) is the primary metabolic derangement in disorders of fatty acid oxidation.	
Blood gas & Anion Gap	([Na+ + K+] - [Cl- + HCO3-] (*normal <12 mmol)* Metabolic acidosis with an elevated anion gap is seen in the organic acidaemias such as propionic academia.	
Ammonia	Metabolically, hyperammonaemia is seen primarily with urea cycle disorders, organic acidaemias and fatty acid oxidation disorders (FAOD).	
Ketones (blood and urine)	Ketosis/ketonuria is a prominent feature of some metabolic disorders, such as organic acidaemias. Fatty acid oxidation disorders (FAOD) and hyperinsulinism cause hypoketotic hypoglycaemia.	
Lactate	***Elevated lactate is most commonly a marker of hypoxia and poor tissue perfusion.*** However, mitochondrial disorders are often associated with elevated blood or cerebrospinal fluid lactate in an elevated ratio to pyruvate (>20).	
Plasma Urea & creatinine, electrolytes	**Liver function tests & Clotting screening**	**Creatine Kinase, Calcium**

7.1 HYPERAMMONAEMIA

- Elevated ammonia concentrations can cause acute encephalopathy.
- Normal values should be less than 50 □mol/l (<100 in the first month of life) but mildly raised values can be observed due to false positive values caused by inaccurate sampling (squeezed sample, sample not stored on ice, sample not processed qithin 30 minutes of collection).

- Artifactually high values can be caused by haemolysis, or delay in separating the sample.
- Hyperammonaemia requires emergent intervention because a lack of treatment can result in permanent brain injury and death.
- Capillary samples are often haemolysed or contaminated and therefore should not be used.

Repeat plasma ammonia immediately if >100 □mol/l in children, >150 □mol/l in neonates
(to recheck always rapidly if elevated)



8 Initial management

Refer early to PaNDR for advice (01223 274 274)

Is this a TIME-CRITICAL TRANSFER?
Hyperammonaemia needs URGENT discussion with Metabolic team and PaNDR

A. Support A-B-C-D

- If profound encephalopathy, intractable seizures, or recurrent apneas, intubate and start mechanical ventilation
- If signs of acute circulatory failure, start fluid resuscitation with balanced crystalloids (up to 40-60 ml/kg)

- If signs of refractory circulatory failure despite initial intravascular fluid expansion, consider start peripheral inotropic support (adrenaline or dopamine) while more definitive central access is achieved.
- If seizures, treat as per APLS
- Consider neuroprotection if signs of cerebral edema and raised ICP

B. If signs of infection, start ATB as per local policy (consider adding Acyclovir)

C. Stop any source of protein intake (feeds or TPN)

- Insert NGT or OGT and keep the patient NBM
- Start peripheral dextrose infusion with electrolytes (0.45% sodium Chloride)

D. Drive Anabolism (to stop further fatty-acid oxidation or protein breakdown)

- If hypoglycaemia, give dextrose 10% 2.5 ml/kg as an IV bolus
- Start dextrose infusion (10% dextrose) at a rate to provide 8-9 mg/kg/min (see www.bimdg.org.uk for drug-infusion calculations)
- If hyperglycaemia persistently > 10 mmol/l, start insulin infusion according to the local diabetic protocol rather than reducing the glucose intake.

E. Correct acidosis if present

- Consider sodium bicarbonate after discussion with Metabolic team

F. Remove toxin substance (ammonia)

- Start IV ammonia scavengers always after discussion with the Metabolic team
- Ensure samples have been taken prior to starting the therapy
- In an emergency the loading dose should be given initially followed by the maintenance dose (see table below based on www.bimdg.org.uk)
- These drugs should be given as soon as possible as a continuous intravenous infusion.
- Sodium benzoate and sodium phenylbutyrate can be given together: the maximum concentration for infusion being no more than 2.5 gram of each drug into 50ml of 5% or 10% dextrose
- N-carbamyl glutamate (Carbaglu) can be given (250mg/kg orally) in some specific indications following advice from the Metabolic team

Drug	Loading dose over 90 minutes	Maintenance dose over 24 hours	Maximum daily dose (every 24 hours)
Sodium Benzoate	250 mg/kg	250 mg/kg/24h	500 mg/kg

Sodium phenylbutyrate	250 mg/kg	250 mg/kg/24h	600 mg/kg
Arginine	150 mg/kg	300 mg/kg/24h	500 mg/kg
Carnitine**	100 mg/kg	100 mg/kg/24h	300 mg/kg

Carnitine should NOT be given if there is evidence of a cardiomyopathy, any cardiac arrhythmia or if a long chain fatty acid oxidation disorder is suspected

9 Transport considerations

If Time-critical transfer is advisable for early renal replacement therapy, local referring team may need to mobilise promptly

- Ensure ETT is well secured and in good position in CXR if patient intubated
- Ensure adequate monitoring for transport (continuous ECG, ETCO2, SaO2, frequent NIBP or continuous invasive BP)
- Ensure patient is sedated and muscle relaxed for transport if patient intubated (check pupils, HR and BP as surrogate for seizure activity)
- Prepare fluid boluses
- Consider preparing inotropic infusions ready to commence if necessary
- If possible, local team to collect tube sample prior to start any treatment:
    i. Plasma amino acids (lithium heparin)
    ii. Urine amino acids & Organic acids
    iii. Urine organic acids including urine orotic acid
    iv. Carnitine profile ("Guthrie" card)
    v. DNA sample for storage (EDTA) if patient not transfused

10 Monitoring compliance with and the effectiveness of this document

See appendix 2 (an extract from the developing Trust documents policy) for notes on how to complete this section.

11 References

- Rice, G. M.; Steiner, R. D. (2016). Inborn Errors of Metabolism (Metabolic Disorders). Pediatrics in Review, 37(1), 3–17. doi:10.1542/pir.2014-0122
- Jeanmonod R, Asuka E, Jeanmonod D. Inborn Errors Of Metabolism. [Updated 2021 Nov 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459183/
- Undiagnosed Hyperammonaemia: Diagnosis and Immediate Management. British Inherited Metabolic Disease Group website and guidelines.

https://bimdg.org.uk/store/guidelines/Hyperammonaemiaand_manage_2016_415469_09092016.pdf

- Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, Mandel H, Martinelli D, Pintos-Morell G, Santer R, Skouma A, Servais A, Tal G, Rubio V, Huemer M, Dionisi-Vici C. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019 Nov;42(6):1192-1230. doi: 10.1002/jimd.12100.

12 Associated documents

List supporting documents to be read in conjunction with this document, eg:

- developing Trust documents policy

Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

Disclaimer

It is **your** responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

Document management

The table below will be completed by the Trust documents team:

Approval:	Via PaNDR Governance March 2022		
JDTC approval:	14/06/2022		
Owning department:	Paediatric and Neonatal Decision Support and Retrieval Service		
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Version number:	1	Review date:	
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Appendix 1: Table 1. Summary of Clinical features and management of IEM

	FATTY ACID OXIDATION DISORDERS	ORGANIC ACIDEMIAS	AMINOACIDOPATHIES	UREA CYCLE DISORDERS
Metabolism	**Fat** Defect in b-oxidation of fatty acids.	**Protein** Defect in amino acid breakdown leads to accumulation of organic acid metabolites	**Protein** Defect in amino acid breakdown leads to accumulation of certain intact amino acids	**Protein** Defect in making urea (blood urea nitrogen) from ammonia that results from amino acid breakdown
Disorders (non-exhaustive list)	Medium-chain acyl CoA dehydrogenase deficiency Long-chain 3-hydroxy acyl CoA dehydrogenase deficiency Very long-chain acyl CoA dehydrogenase deficiency	Propionic Methylmalonic Isovaleric acidaemias	Maple Syrup Urine Disease (MSUD)	Ornithine transcarbamylase deficiency (X-linked) Citrullinaemia Arginosuccinic aciduria
Presentation	**Hypoketotic Hypoglycemia** Lethargy, vomiting Sudden infant death syndrome, Reye syndrome Cardiomyopathy & rhabdomyolysis (Long-chain disorders)	**Metabolic Acidosis with Anion Gap** **Elevated Ketones** Neonatal lethargy, vomiting, coma, strokes, death	**No Acidosis or Hyperammonaemia** Elevations in specific aminoacids *See text for clinical features*	**Hyperammonaemia Without Acidosis** Neonatal lethargy, vomiting, seizure, coma, death

Lab tests	Newborn Screen Plasma acylcarnitines Hypoglycaemia No or inappropriately low ketones	Newborn Screen Urine organic acids Plasma acylcarnitines	Newborn Screen Plasma amino acids (PAA)	Newborn Screen (not for ornithine transcarbamylase deficiency) Hyperammonaemia Plasma amino acids Urine orotic acid
Acute treatment	Dextrose (10% with salt, , 20-25% if central access))) Stop lipids Riboflavin Early use of fluids to prevent hypoglycaemia Echocardiography for long-chain fatty acid oxidation Carnitine if defieicny and no cardiomyopathy Ketones	Dextrose (10% with salt, , 20-25% if central access)) Early use of fluids Alkalanisation (BiNa, THAM) No protein Intravenous lipid emulsion Hemodialysis may be needed in sick neonate	For maple syrup urine disease, similar to organic acidaemias Avoid hyponatraemia	Stop proteins Dextrose (10% with salt, 20-25% if central access) Early use of fluids Sodium benzoate/ phenylacetate Arginine Hemodialysis
Chronic treatment	Low-fat diet Avoid prolonged fasts Night-time feedings when sick Carnitine	Low-protein diet Supplemental medical food Carnitine Liver transplantation	Restrict offending amino acid Supplemental food Monitor plasma amino acids	Low-protein diet Supplemental food Phenylbutyrate Arginine/citrulline Liver transplantation

Appendix 2: Monitoring compliance and effectiveness

Set out below are the issues which **must** be addressed when drawing up the monitoring section of a Trust document. It is important that a suitable process is chosen, one which will be followed through in practice and is appropriate for the document in question.

Note: It is not necessary to reproduce the questions below in the document but it is crucial that all the listed topics are covered. The questions and responses are for guidance only.

1. **What are the key standards of the document that will be monitored?**
   This should include the standards laid down in the document or any key performance indicators (KPIs), such as indicated by the NHS Litigation Authority or any other relevant external bodies (as appropriate).
2. **How will these standards or KPIs be monitored?**
   Consider what will be done in practice to monitor what is described in the document. The following is a list of suggestions which may be useful:
   - a formal audit (internal or external)
   - quarterly spot checks
   - review of reported incidents
   - inspections
   - risk assessments or risk reviews
   - patient/staff surveys
   - complaints monitoring
   - sickness/ absenteeism levels
   - training records.

   An example of a KPI might be that '85% of all patient complaints are resolved within 14 days' or that '95% of patients surveyed are happy with the service received.' The KPI will vary according to the practice area and document type.
3. **Who will be responsible for conducting the monitoring?**
   Please state in the document, for each type of monitoring listed, whether it is an individual (no names needed, just the job title) or a group or committee who will be responsible.
4. **How frequently will the standards or KPIs be assessed?**
   Please state how often the monitoring will take place: eg daily, weekly, monthly, quarterly, annually or by spot checks.
5. **Who will review the results of the monitoring?**
   Please state who will be responsible for looking at the results of the monitoring; identifying any shortfalls which come to light, and most importantly, what will be done to address any shortfall.

6. **Responsibility for implementation of any actions needed**.
   Once actions have been identified as a result of (5) above, whose responsibility will it be to ensure any actions are followed through? Will it be an individual or a committee or group? – please state which. Please also state how the results of any implementation will be recorded or evidenced.