CoMET Paediatric Metabolic Emergencies

This guideline is for use by healthcare staff, at CoMET undertaking critical care retrieval, transport and stabilization of children, and young adults.

CoMET is a Paediatric Critical Care Transport service and is hosted by the University Hospitals of Leicester NHS trust working in partnership with the Nottingham University Hospitals NHS Trust.

The guidance supports decision making by individual healthcare professionals and to make decisions in the best interest of the individual patient.

This guideline represents the view of CoMET, and is produced to be used mainly by healthcare staff working for CoMET, although, professionals, working in similar field will find it useful for easy reference at the bedside.

We are grateful to the many existing paediatric critical care transport services, whose advice and current guidelines have been referred to for preparing this document. Thank You.

Executive Lead/ Medical Director:	**Andrew Furlong (LRI, UHL – andrew.furlong@uhl-tr.nhs.uk)**
Author:	**Zoe Hahn – Deputy sister, CoMET** **Zoe.hahn@uhl-tr.nhs.uk** **Mohammed Rohouma – Registrar, CoMET** **Mohammed.rohouma@uhl-tr.nhs.uk**
Guideline Lead:	**Mohammed Zoha – CoMET Consultant** **Mohammed.zoha@uhl-tr.nhs.uk**
Clinical Lead:-	**Georgina Harlow – CoMET Clinical Lead** **Georgina.harlow@nuh.nhs.uk** **Georgina.harlow@uhl-tr.nhs.uk**
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Education and Training

1. Annual Transport team update training days
2. Workshops delivered in Regional Transport Study days/ Outreach

Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Incident reporting	Review related Datix	Abi Hill – Lead Transport Nurse abi.hill@uhl-tr.nhs.uk	Monthly	CoMET Lead Governance Meeting
Documentation Compliance	Documentation Audit	Abi Hill – Lead Transport Nurse abi.hill@uhl-tr.nhs.uk	3 Monthly	CoMET Lead Governance Meeting

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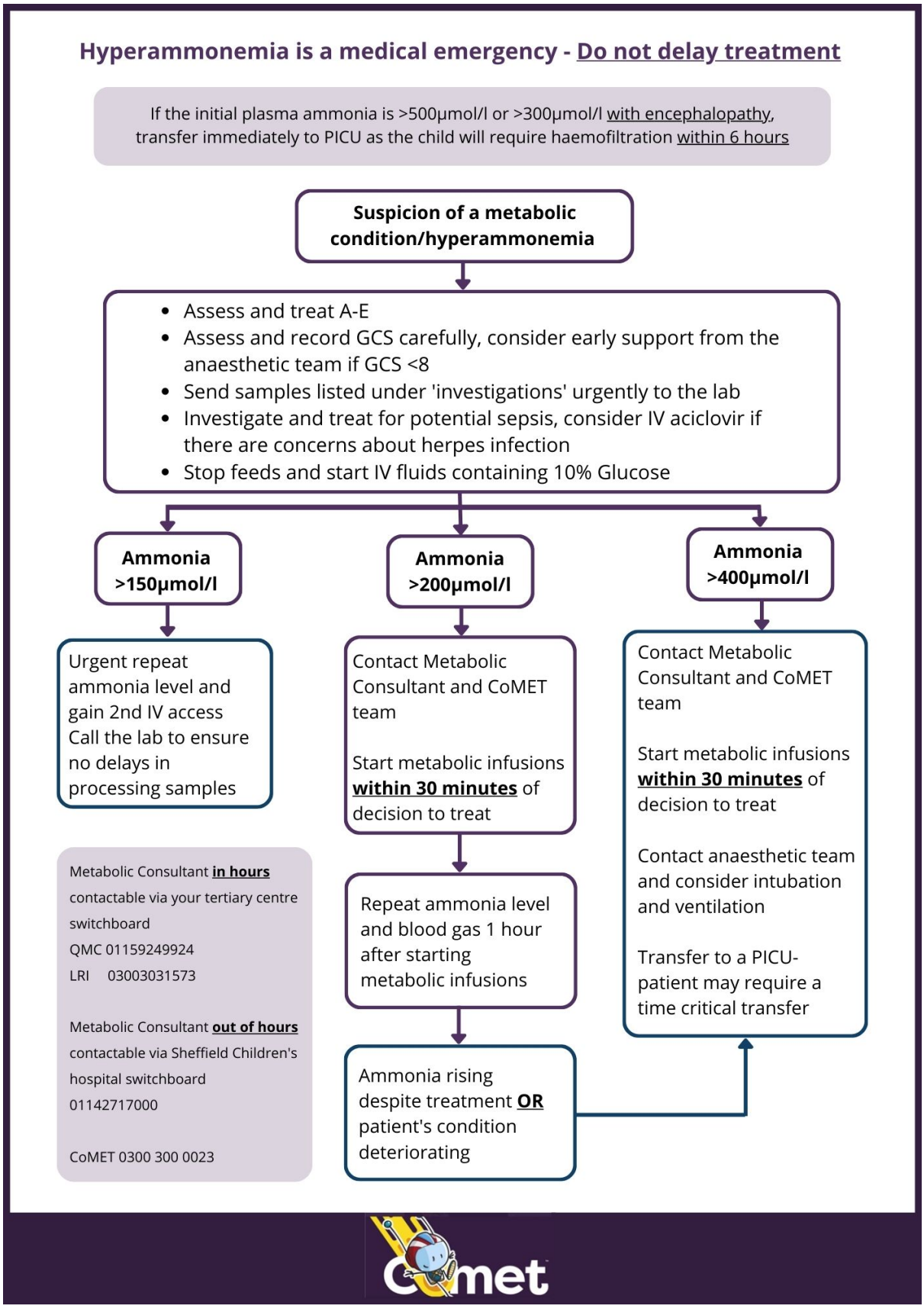

2. Introduction

Inborn Errors of Metabolism (IEM) encompass a large group of individually rare disorders and can present as acute metabolic emergencies. They often result in significant morbidity and mortality therefore rapid recognition and instigation of treatment is essential. Managing metabolic disorders can be very complicated, it is best to seek early help from a specialist metabolic team if a metabolic emergency is suspected.

Children with a metabolic disorder often present with non-specific symptoms. The most common presentations are hyperammonaemia, metabolic acidosis with an expanded anion gap and hypocalcaemia. The most common acute clinical presentations include progressive encephalopathy. Children with metabolic disorders are at great risk of decompensation during episodes of illness and therefore need careful management to ensure they receive the optimum care to avoid states of catabolism[1]

3. Clinical Presentation[1,2,3,5,6]

In the neonatal period:

- Poor sucking
- Lethargy
- Hypotonia (central) with peripheral hypertonia
- Respiratory distress
- Vomiting
- Dehydration
- Seizures
- Involuntary movements (boxing, cycling or slow limb elevation, myoclonic jerks)
- Coma
- Abnormal urine odour

After the neonatal period, in addition to above:

- Encephalopathy
- Ataxia
- Focal neurological signs
- Intracranial hypertension
- Agitation/confusion
- Cyclical/recurrent vomiting

4. Investigations For Suspected Inborn Errors of Metabolism[2,3,5]

Investigations should be sent to the lab urgently. Please discuss this with the duty biochemist.

Blood:

- FBC
- Clotting
- Glucose, Lactate*, free fatty acids and 3-hydroxybutyrate

- LFT, U&E, bone profile, CK, Plasma amino acid profile and cortisol
- Ammonia* and Acylcarnitines
- Venous blood gas
- Point of care glucose and ketones
- Blood culture
- Consider hypoglycaemia screen if blood glucose is <2.6mmol/l

***Ammonia sample must be hand delivered to the lab immediately, call ahead to let them know you are taking a sample.**

*Please note that plasma ammonia and lactate may be artefactually raised if the sample is haemolysed or the limb has been excessively squeezed during blood taking. Check with the lab for evidence of haemolysis and aim for free flowing samples.

Urine:

- Organic acids and amino acids (Urine Inborn Error screen)
- Point of care Ketones

CSF- If an LP is undertaken as part of a septic screen, consider adding:

- **DO NOT DO AN LP IF PATIENT IS ENCEPHALOPATHIC**
- Glucose and lactate
  (Take plasma sample for lab glucose immediately before LP)
- Amino acids- glycine, threonine, serine
  (Take plasma sample for amino acids around the same time as the LP)

5. Initial General Management of All Patients Suspected of Presenting Acutely With An Inherited Metabolic Disease[5,8]

Children who have a known metabolic condition will often have their own emergency management plan, for support speak with their named metabolic team.

- Stop feeds.
- Give 2ml/kg bolus of 10% glucose IV initially (equal to 200mg/kg)
- Give 10ml/kg 0.9% sodium chloride bolus (20ml/kg if shocked) and reassess the need for further fluid boluses
- Continue with 10% Glucose at 5mls/kg/hr until the next solution is ready
- **Metabolic infusions *(usually Sodium Benzoate, Sodium Phenylbutyrate, Arginine and Carnitine)*** should be given as soon as possible, the doses and administrations are outlined in the drug monograph in section 8 of this guideline
- **Ongoing Fluid Management***:*

Amount: Maintenance plus deficit for dehydration
Type: 0.9% Sodium Chloride + 10% Glucose in General Metabolic emergencies
If Hyperammonaemic on FULL doses of metabolic infusions: Plain 10% Glucose. (Use 0.18% Sodium Chloride and 10% Glucose if not on full dose of metabolic infusions)
Additives: Potassium Chloride if passing urine and normal Potassium level.

- **Check blood sugar hourly**. Aim to keep blood sugar in the range 6 – 10mmol/l. If plasma glucose exceeds 14mmol/L and there is glycosuria, start IV **Insulin infusion** rather than

reducing the glucose intake. Start at 0.025units/kg/hour, may need to increase to 0.3units/kg/hour to control hyperglycaemia. If there is evidence of lactic acidosis seek advice from a metabolic consultant before giving insulin (lactic acidosis can be exacerbated by insulin and it may be necessary to reduce the concentration of the glucose infusion in this circumstance)

- Treat any infection and constipation (which increases ammonia absorption from the gut). Lactulose is recommended as theory suggests this will be beneficial although, as yet, this is unproven

It is important to assess patients for encephalopathy by recording a GCS on presentation and carefully reassessing, as this allows for timely recognition of deterioration.

Birmingham Children's Hospital - 0121 333 9999
Great Ormond Street Hospital - 020 7405 9200
Leicester Royal Infirmary- 03003031573
Royal Manchester Children's Hospital - 0161 276 1234
Queens Medical Centre- 01159249924

6. Hyperammonaemia[5]

Hyperammonaemia is a medical emergency and treatment should not be delayed. Metabolic infusions (Sodium benzoate, Sodium phenylbutyrate, Arginine and Carnitine) should be sourced and given as soon as possible. Doses and instructions for administration can be found in section 8 of this guideline. Normal ammonia values should be less than 50μmol/l but mildly raised levels are common.

In addition to the general management mentioned above:

- If the initial plasma ammonia level is >150μmol/l urgently repeat the level, undertake investigations outlined in this guideline, and obtain a second IV access.
- If the repeat level remains between 100-200 μmol/l seek advice from a metabolic consultant before giving any ammonia specific therapy as the patient may be suitably managed using nutritional therapy
- For ammonia levels >200μmol/l start metabolic infusions as soon as possible and contact a metabolic consultant and the CoMET team for advice.
- Consider a single oral dose of N-Carbamyl glutamate (Carglumic acid) with advice from the metabolic consultant
- Give IV maintenance fluids + any fluid deficit as outlined in section 5 of this guideline
- If the ammonia level is >500μmol/l or >300μmol/l with encephalopathy the child will need a time critical transfer to metabolic centre as they will require haemofiltration within 6 hours
- Avoid hyperventilation as alkalosis enhances ammonia toxicity
- Avoid giving bicarbonate if pH is >7.2

7. Metabolic Acidosis[7]

If the metabolic acidosis is due to Diabetic Ketoacidosis, please refer to the DKA guidelines.

For children presenting with a persistent metabolic acidosis and an increased anion gap stop feeds and start IV maintenance + fluid deficit as outlined in section 5 of this guideline. Discuss with metabolic consultant. Carnitine, Hydroxocobalamin and Biotin should be given, see drug monograph in section 8 for dosing and administration information.

If the metabolic acidosis does not correct with IV glucose therapy and bicarbonate corrections discuss with the metabolic consultant and CoMET team. Haemofiltration may be required.

If the anion gap is not increased the acidosis may be caused by bicarbonate loss and should therefore be treated with bicarbonate replacement. Look for Renal or Gastrointestinal losses.

Anion gap = $[Na^+]$ - ($[Cl^-]$ + $[HCO_3^-]$) *(Normal Range 10-16)*

8. Emergency Metabolic Drug Monographs

Drug	Dose	Administration
L- Arginine Injection	**Neonate and Child**: IV loading dose: 300mg/kg followed by continuous infusion Continuous IV Infusion: 300mg/kg/day (increased if necessary up to 600mg/kg/day if <40kg, or 504mg/kg/day if >40kg) Infusion rate (ml/hr) = $\frac{\text{Dose (mg/kg/hr) x patient weight (kg)}}{\text{Concentration (mg/ml)}}$	Loading dose: IV infusion over 90 minutes Dilute to 100mg/ml in Glucose 10% Continuous IV infusion: Dilute to 50mg/ml with 10% glucose (maximum concentration for peripheral administration)
Biotin Injection	**Neonate – 18 years**: IV Bolus: 5 – 50mg/day	IV bolus injection over 3 to 5 minutes *(IM injection can be given intravenously)*
Biotin Tablets	**Neonate – 18 years**: Enterally: 5 – 50mg/day	Tablets may be crushed and mixed with water
Carnitine Injection (Levo-carnitine)	**Should not be used if suspected LCFA disorder, cardiomyopathy or cardiac arrhythmia- discuss with metabolic consultant first** **Neonate – 18 years:** IV loading dose: 100mg/kg followed by continuous infusion Continuous IV Infusion: 100mg/kg/day (max 300mg/kg/day)	Loading dose: IV Infusion over 30 minutes Can be given neat or diluted in Sodium Chloride 0.9%, glucose 5% or glucose 10% Continuous IV Infusion: Dilute in sodium chloride 0.9%, glucose 5% or 10%

	OR IV Bolus: 25mg/kg QDS Infusion rate (ml/hr) = $\frac{\text{Dose (mg/kg/hr) x patient weight (kg)}}{\text{Concentration (mg/ml)}}$	IV bolus injection: Given over 5 to 10 minutes Can be given neat or diluted in Sodium Chloride 0.9%, glucose 5% or glucose 10%
Hydroxocobalamin (VitB12) Injection	**Neonate – 18 years**: IV or IM: 1mg once daily (for 5 days and then review)	IV slow bolus Injection *(IM injection can be given intravenously)*
Sodium Benzoate Injection	**Neonate – 18 years**: IV Loading dose: 250mg/kg followed by continuous infusion Continuous IV infusion: 250mg/kg/day (maximum 500mg/kg/day) Infusion rate (ml/hr) = $\frac{\text{Dose (mg/kg/hr) x patient weight (kg)}}{\text{Concentration (mg/ml)}}$	Loading dose: IV Infusion over 90 minutes Dilute to 50mg/ml in Glucose 10% Continuous IV Infusion: Dilute to a maximum concentration of 50mg/ml with 10% glucose

Sodium Phenylbutyrate Injection	**Neonate – 18 years:** IV loading dose: 250mg/kg followed by continuous infusion Continuous IV infusion: 250mg/kg/day (maximum 600mg/kg/day) $\text{Infusion rate (ml/hr)} = \frac{\text{Dose (mg/kg/hr) x patient weight (kg)}}{\text{Concentration (mg/ml)}}$	Loading dose: IV infusion over 90 minutes Dilute to 50mg/ml in Glucose 10% Continuous IV Infusion: Dilute to a maximum concentration of 50mg/ml with 10% glucose
Carglumic Acid Dispersible Tablets	**Neonate – 18 years:** 250mg/kg as a single EMERGENCY ENTERAL DOSE and then to be reviewed by metabolic consultant. Usual maintenance dose 50-125mg/kg twice daily	Tablets may be halved and quartered Round dose down to the nearest 50mg To administer disperse tablet in 5 – 10mls of water

Follow this link from the BIMDG website for more information and calculators for making up the infusions:
http://www.bimdg.org.uk/store/guidelines/Drug_Calculator_Index_743383_12042017.pdf

***IV Compatibilities: Sodium benzoate, arginine, carnitine and sodium phenylbutyrate can be infused together at Y-site along with maintenance fluids which contain* GLUCOSE, SODIUM CHLORIDE AND POTASSIUM CHLORIDE. Please contact pharmacy for further information on IV compatibilities.**

9. Location of Metabolic Drugs

Hospital	Drugs Stocked	Location
Kettering General	**No drugs stocked**	**Consider contacting Northampton Pharmacy for shipment**
King's Mill	Arginine, Biotin, Carnitine, Hydroxocobalamin, Sodium Benzoate, Sodium Phenylbutyrate. ***Carglumic acid**	Emergency drug box in Room 2 on the Neonatal Unit ***Request from Pharmacy**
Leicester Royal Infirmary	Arginine, Sodium Benzoate, Sodium Phenylbutyrate. ***Biotin, Carnitine, Carglumic acid**	CICU (Level 4 - Balmoral) "Scavenger box" ***Request from Pharmacy**
Lincoln County	Arginine, Biotin, Carglumic acid, Carnitine, Hydroxocobalamin, Sodium Benzoate, Sodium Phenylbutyrate	Emergency drug box on the Neonatal unit (Some drugs may also be kept on the Children's Ward)
Northampton General	Arginine, Carnitine, Hydroxocobalamin, Sodium Benzoate, Sodium Phenylbutyrate ***Biotin, Carglumic acid**	Emergency Drug Cupboard and Pharmacy ***Not available**
Pilgrim	Arginine, Biotin, Carglumic acid, Carnitine, Hydroxocobalamin, Sodium Benzoate, Sodium	Children's ward 4A

	Phenylbutyrate	
Queens Hospital Burton	Arginine, Carglumic acid, Carnitine, Hydroxocobalamin, Sodium Benzoate, Sodium Phenylbutyrate	Some stock available from Pharmacy - anything that isn't available can be requested from Royal Derby Hospital and transported
Queens Medical Centre	Arginine, Carnitine, Hydroxocobalamin, Sodium Benzoate, Sodium Phenylbutyrate. ***Biotin, Carglumic acid**	Ward D33 (East block level D) ***Request from Pharmacy**
Royal Derby	Arginine, Biotin, Carglumic acid, Carnitine, Hydroxocobalamin, Sodium Benzoate, Sodium Phenylbutyrate	All available by request from ~~to~~ Pharmacy

Appendix: Interpretation of laboratory results - RCH Clinical Handbook 7th Edn, 2003, Blackwell Science. Metabolic Conditions (p475)[4]

Metabolic condition	pH	Glucose	Ketones	Ammonia
Urea cycle defects	N or ↑	N	N	↑↑
Organic acidaemia	↓	↑, N or ↓	N or ↑	↑
Ketolysis defects, MSUD^	N or ↓	N or ↑	↑↑	N
FA oxidation defects	N or ↓	N or ↑	N or ↓	N or ↑
Hyperinsulinaemia	N	↓↓	N	N or ↑
Pituitary/adrenal deficiency	N	↓	↑	N

N= Normal

References

1. Kripps, K.A., Baker, P.R., Thomas, J.A., Skillman, H.E., Bernstein, L., Gaughan, S., Burns, C., Coughlin, C.R., McCandless, S.E., Larson, A.A., Kochar, A., Stillman, C.F., Wymore, E.M., Hendricks, E.G., Woontner, M. and Van Hove, J.L.K. (2021) Review: Practical strategies to maintain anabolism by intravenous nutritional management in children with inborn metabolic diseases. Molecular Genetics and Metabolism (online).
2. Saudubray J-M, Baumgartner M, Walter J (Eds.). Inborn Metabolic Diseases Diagnosis and Treatment 6th edition; 2016.
3. Melbourne, T., 2022. Clinical Practice Guidelines: Metabolic disorders. [online] Rch.org.au. Available at: https://www.rch.org.au/clinicalguide/guideline_index/Metabolic_disorders/
4. RCH Clinical Handbook 7th Edn, 2003, Blackwell Science.
5. British Inherited Metabolic Disease Group: Undiagnosed hyperammonaemia. Diagnosis and immediate management, 2008.
6. North West & North Wales Paediatric Transport Service. Guidelines for the Management of Neonatal and Paediatric Hyperammonaemia, 2018.
7. SC(NHS)FT Investigation of Suspected Inherited Metabolic Disorders 2019 (CAEC ID 1067)
8. Sheffield Children's Hospital's: 'Guideline for the Emergency Treatment of Inborn Errors of Metabolism'