Paediatric Intensive Care Unit

Hyperammonemia

Staff relevant to:	UHL Paediatric Intensive Care Unit
Approval date:	February 2025
Version:	4
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Written by:	J Vujcikova
Trust Ref:	C50/2016

1. Introduction and Who Guideline applies to

This guideline is for use within the UHL Paediatric Intensive Care Unit. 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.

This clinical guideline is based on available evidence in conjunction with clinical expertise and experience. 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.

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2. Guideline Standards and Procedures

Normal values should be less than 50 µmol/l but mildly raised values are common – up to 80 µmol/l. Artefactual high values can be caused by muscle activity, haemolysis or delay in separating the sample. Capillary samples are often haemolysed or contaminated and therefore should not be used.
Values up to 80 µmol/l are common in patients with urea cycle disorders, even those with good metabolic control.
In neonates any illness may be responsible for values up to 180 µmol/l.
In any patient values **in excess of 200 µmol/**l require urgent attention.

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 [15]. Therefore, patients with ammonia >440µmol/l resistant to pharmacological treatment must start renal replacement therapy in form of haemodialysis/haemofiltration within 6 hours of identification. [14, 15]See flowchart for summary in appendix

2.1 Clinical symptoms and diagnosis:

Hyperammonaemia associated with inherited disorders of amino acid and organic acid metabolism is usually manifested by signs of an acute encephalopathy (irritability, somnolence, vomiting, seizures, and coma). Although the majority of these patients present in the newborn period, metabolic crisis with hyperammonaemia may also occur in childhood, adolescence, and adulthood.
Metabolic conditions affecting fatty-acid oxidation can also present with cardiomyopathy and pulmonary haemorrhages.

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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.
The most frequent symptoms are:

- failure to thrive,
- persistent vomiting,
- developmental delay,
- behavioural changes.

Persistent hyperammonaemia, if not treated rapidly, may cause irreversible neuronal damage.
After the diagnosis of hyperammonaemia is established in an acutely ill patient, certain diagnostic tests should be performed to differentiate between urea cycle defects and other causes of hyperammonaemic encephalopathy such as a liver failure or an infection. In a patient with a presumed inherited metabolic disorder, the aim of therapy should be to normalise blood ammonia levels.
Ammonia is neurotoxic and causes cerebral oedema. Degree and duration of hyperammonaemia directly correlate with prognosis. There was research suggesting that pH of blood affects ammonia transport into the brain and that acidosis is protective while alkalosis increases ammonia transport into the brain. However, the recent reports did not confirm that theory. (1)

PROGNOSIS:

The degree of neurologic dysfunction of the patient is related to the duration of cerebral oedema and peak ammonia level. Most children will have cognitive impairment, but early treatment to remove ammonia and other metabolites from the bloodstream will lessen the severity of this impairment.

Prognosis is considered poor if:

1. Hyperammonaemic coma has lasted more than 3 days
2. Intracranial pressure is clearly increased
3. Ammonia peaked at >1000 µmol/L although the impact of this level on prognosis depends on the duration of hyperammonaemia [2,3,4]

If ammonia > 350 µmol/l (10x normal) significant CNS deficit observed. [5]
Good outcome if ammonia < 250 µmol/l or coma resolved < 48h of onset of symptoms. (Walter 2000)
More likely to die if ammonia > 1000 µmol/L. [6]
Peek ammonia > 200 µmol/l within 48 hrs independent risk factor for mortality. [7]

DIFFERENTIALS

- Inborn Errors of Metabolism
  - Urea Cycle Defects

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- Enzymes e.g. OTC deficiency
- Transport e.g. LPI, HHH
- Organic Acidaemias
- Fat Oxidation Defects
- Pyruvate Carboxylase deficiency
- OAT deficiency (neonates/infants)
- HIHA

- Transient Hyperammonaemia of the Newborn (characterised by a normal glutamine level)
- Infection, e.g. Proteus, Klebsiella, Herpes simplex (especially in neonates)
- Liver failure
- Portosystemic Shunt (Is ductus venousus in neonates open?)
- Protein load & catabolism, eg trauma, burns
- GI bleed
- Drugs or metabolites interfering with urea cycle function: Leukaemia treatment with Asparaginase, Valproate, Carbamazepine, Topiramate, certain types of the chemotherapy

LABORATORY TESTS:

Make sure that sample is "free-flowing" and transported ON ICE to the laboratory and investigated IMMEDIATELY! IT IS TIME CRITICAL EMERGENCY! Heal pricks, squeezed samples, samples at room temperature, and delays in processing will give a falsely raised result.

- Ammonia > 150µmol/L repeat sample
- Ammonia > 200 µmol/L, start treatment and repeat sample

Seek urgent metabolic opinion – Sheffield Children's Hospital offers us 24h advice service (contact number: switchboard tel: 011420271207000)

• gas, glucose, U&E, plasma ammonia, plasma aminoacids, blood ketones
• urine organic acids, urinanalysis (including ketones), urine orotic acid.
• liver function test (AST, ALT, ALP, Bi), cholesterol, triglycerides
• plasma acylcarnitines
• newborn screening sample
• blood, urine and or CSF culture - ! CEREBRAL OEDEMA IS CONTRAINDICATION FOR LP!
• the liver US - is ductus venosus open?
• a sample for genetics

Presence of respiratory alkalosis in a sick hyperammonaemic neonate is an indicator of an underlying urea cycle defect. Hyperammonaemia with metabolic acidosis is more likely to be due to an organic acid disorder.

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!!! Sepsis should be always kept as the first consideration or possible potentiating factor in the situation of the metabolic crisis! And vice versa: ! In any newborn with clinical distress resulting in the suspicion of sepsis, hyperammonaemia should be considered from the very beginning!!!

Continue with monitoring of glucose hourly, ammonia and gas with lactate 3 hourly, U&E 6 hourly, neuro obs hourly including GCS.

2.2 TREATMENT:

Immediate treatment of hyperammonaemia is crucial to prevent neurologic damage.

1. **Assess ABC...**

2. **Stop oral intake (this reduces further protein load) and insert IV access.**

3. **Treat Hypoglycemia**. Give bolus 2ml/kg of 10% glucose. (Glucose will stimulate insulin release and turn off catabolism)

4. **Consider fluid bolus 10 - 20ml/kg of 0.9% Sodium chloride** and assess the response (HR, BP, perfusion, and liver size). If peripheral circulation is poor or child clinically shocked, further resuscitation with volume and/or inotropic support is needed. Keep in mind that circulation needs to be stabilised; however, fluid overload worsens potential brain oedema.

5. **Continue with 10% glucose 5ml/kg/h IV until further plan is established** (potential intubation, CVL insertion, exact calculations done – maintenance fluid, dehydration) and metabolic team contacted. [13]

6. Maintenance fluids: 10% glucose + 0.9% saline; 100% intake based on Holliday - Segar formula; 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

7. **Start IV Antibiotics based on Sepsis UHL Childrens Hospital Guideline**:Consider IV Aciclovir if concerns for herpes infection (send investigations).

8. Check blood glucose hourly, target 6 - 10mmol/L; to reverse catabolism provide adequate caloric intake.

9. Initially attempt 80 kcal/kg/day; build up to120 kcal/kg/day; 10-20% glucose with aim 10-15mg/kg/min for infant/neonate (1g glucose = 3.4kcal) calculation: glucose mg/kg/min = (ml/h x %gluc) / (6 x kg)

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- volume adjust according fluid allowance (fluid restriction is recommended in brain oedema cca 2/3 of maintenance, once cvvh has been commenced fluid intake can be liberalised)

- be careful with sodium as Sodium benzoate and phenylbutyrate contain a high sodium concentration (1 gram of sodium benzoate contains 7 mmol of sodium; 1 gram of sodium phenylbutyrate 5.4 mmol of sodium)

- max concentration of glucose to peripheral IV is 12.5%; for higher concentration a central access is required

- Hyperglycaemia (> 14mmol/L & glycosuria) should be corrected with Insulin to support anabolism (start 0.025units/kg/h and titrate to blood glucose levels); DO NOT DECREASE % OF GLUCOSE! (unless lactate is rising - discuss with the Metabolic team), monitor blood glucose a 30 min, if insulin commenced

- if stable consider Intralipid 1-3g/kg/d (1g lipid = 9kcal) after ruling out fatty acid oxidation defect.

  Example: 3kg infant with fluid restriction to 2/3 of maintenance due to cerebral Oedema.

  Allowance 100ml/kg/d = 300ml (20%G 300ml = 13.8mg/kg/min, 68kcal/kg/d)

STOP ALL PROTEIN INTAKE TEMPORARILY max 48 hours; protein withhold longer than 36-48 hours can promote breakdown of endogenous proteins and hamper metabolic control. Protein intake should be commenced when ammonia returns to < 100 µmol/l within 36 - 48 hours - start at 0.2-0.6g/kg/d - discuss with the Metabolic team. (2)

10. **PROMOTE WASTE NITROGEN EXCRETION:**

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 – get recommendation from Metabolic team, but usually (2, 13): Infusions can be administered peripherally. Infusions are compatible with each other on the same line and with glucose and electrolyte-containing maintenance fluids.

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Tab. 1: Metabolic infusions for children < 10kg

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

*L-carnitine should not be given if there is evidence of cardiomyopathy, any cardiac arrhythmia or if a long chain fatty oxidation disorder is suspected - always discuss with metabolic team.

Tab 2. Metabolic infusion for children > 10kg

	Loading dose	Maintenance dose	Preparation
Sodium Benzoat & Phenylbutyrate	250mg/kg (10ml/kg) over 90 min = run a bag at 6.67ml/kg/h for the first 90 min	0.42ml/kg/h	Use the 1g in 5ml preparations Remove 125ml then add 12.5g (62.5ml) of Sodium Benzoate AND 12.5g (62.5ml) of Sodium Phenylbutyrate to a SINGLE 500ml bag of 10% glucose (to give a solution of approximately 25mg/ml for each medicine)
L- arginine	as per children < 10kg		

• **Sodium benzoate**
250mg/kg/day as loading dose over 90min followed by an ongoing continuous IV infusion 250mg/kg every 24hours until oral treatment (re)initiated. (Max 500mg/kg/d)

• **Sodium phenylbutyrate**
250mg/kg/day as loading dose over 90 min followed by an ongoing continuous IV infusion 250mg/kg every 24 hours until oral treatment (re)initiated. (Max 600mg/kg/d)

• **Arginine** (not in arginase deficiency)[2]
150mg/kg over 90min followed by an ongoing continuous infusion - 300mg/kg every 24 hours until oral treatment (re)initiated (Max 500mg/kg/d). [13]

Refer to relevant IV monographs
Metabolic drug boxes are kept in PED and PICU LRI containing enough medication for the initial dose of sodium benzoate, sodium phenylbutyrate and arginine, allowing time for further stock to be ordered and supplied – discuss with pharmacist urgently.

CONSIDER:

• **Carnitine** in all organic acidurias as it promotes excretion of organic acids[8];
if a fatty acid oxidation defect is suspected, carnitine use may induce arrhythmias!
100mg/kg over 90 min followed by an ongoing continuous infusion -
100mg/kg every 24 hours until oral treatment (re)initiated. (Max 300mg/kg/d)[13]

• **Carglumic acid** (N-carbamyl glutamate) – discuss with on call metabolic team
Consider giving a single dose 250mg/kg PO/NG.
If recommended by metabolic Team - Ongoing dose range: 100-250 mg/kg/day PO/NG divided in 2-4 doses before meals; round total daily dose to nearest 100 mg.

Carnitine and carglumic acid are kept in Windsor Pharmacy LRI and must be ordered via the pharmacist as soon as possible.

• **CVVHD/CVVHDF** - prepare if:

- ✓ <u>ammonia > 400 µmol/L and no response to pharmacological treatment; CVVHD/HD must be started within 6 hours of identification</u>
- ✓ significant encephalopathy (seizures, coma)
- ✓ very early onset of disease (day 1 or 2 of life)
- ✓ neonate/infant with ammonia > 250 umol/L and there is no rapid drop in ammonia level within 3 - 6 hours [2]

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IT IS TIME CRITICAL TO BRING AMMONIA LEVEL DOWN. Ammonia crosses the dialysis membrane rapidly; the higher the flow rate, the higher the clearance. (9)

Insert the biggest Vascath possible Blood flow 6-9ml/kg/min (min 30ml/min HF20); CRRT dose up to 100ml/kg/h; dialysate 50ml/kg/h
Best site to prevent recirculation - ideally IJ
PD is an option but with much lower effectivity, it is no longer recommended
Exchange transfusion causes catabolism, hence is to be avoided.

Most patients will have a slight rise in ammonia after haemodialysis/ CVVHD since removal by scavengers and the liver will not be as effective. This slight rise usually does not necessitate repeat CRRT.

11. **TREAT UNDERLYING PRECIPITANT:**

• infection (do not perform LP if signs of intracranial hypertension/ brain oedema) – IV Antibiotics see – Sepsis UHL Childrens Hospital Guideline - Add IV Aciclovir if herpes is suspected Neonatal Herpes Simplex UHL Childrens Medical Guideline
• dehydration
• drugs interfering with urea cycle function (Asparaginase, Valproate, Carbamazepine, Topiramate)

12. Indication for intubation:

- Coma
- Intractable seizures
- Apnoea
- Circulatory failure
- Need for CRRT and central access insertion

HYPOXIA, HYPOTENSION, HYPERTERMIA, HYPOGLYCAEMIA WORSEN AMMONIA TOXICITY.

13. **NEUROPROTECTIVE STRATEGY - if brain oedema is suspected:**

- Sedation and analgesia – morphine +/-midazolam infusions
- Artificial ventilation - PaCO2 target range 4.5 – 5.5kPa,
- PEEP 5cmH2O (use of PEEP should be individualised to achieve pO2 and pCO2 targets), a tight ventilation control - if manual bagging avoid PaCO2 < 4.0 kPa
- Age appropriate blood pressure to maintain cerebral perfusion pressure (10)
- Avoid hyponatraemia and swings of blood glucose level, monitor osmolarity and avoid fluid overload
- Head up 30 degrees and midline position
- Core temperature 36.0 – 37.5^{o}C

Mannitol is not effective in treatment of brain oedema caused by hyperammonaemia.

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Steroids are to be avoided as they promote catabolism and albumin worsens nitrogen load.

14. **NEUROLOGIC EVALUATION:**

Cerebral studies should be conducted to determine the efficacy of treatment and whether continuation is warranted.

- EEG should be performed to assess both cerebral function and evidence of seizure activity.
- MRI helps predict clinical and neurocognitive outcome. It appears desirable to perform magnetic resonance imaging early on, ideally between days 1 and 4 of each coma or stroke-like episode. (11)
- Evaluation of brain stem function and higher cortical function are useful to assess outcome.

Finally, the decision for continuation is based on baseline neurologic status, duration of the patient's coma and potential for recovery, and whether the patient is a candidate for transplantation. If the basic urea cycle defect is severe enough, liver transplantation should be considered.
Criteria for transplantation are linked back to neurologic status, duration of coma, and availability of donor organs. (12)

Metabolic Team
Dr Forster - Consultant Paediatrician
Siobhan Felix - Children's Metabolic Specialist Nurse
Moira French – Specialist Dietitian
Dr Sharrard – Metabolic Consultant - Sheffield Children's Hospital
On call Metabolic Consultant (24 hour advice) – on mobile via Sheffield Children's Hospital switchboard 0114 2717000

3. Education and Training

Training and raising awareness are on-going processes. On-going awareness is promoted through the induction and continuous bedside teaching. Training is provided for medical staff during lunchtime teaching (Wednesdays) and other sessions, and at junior doctors' induction training. Nursing education is supported by the Practice Development teams, and nursing educators.

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4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Adherence to the guideline	audit	Julia Vujcikova	3 years	CPM

5. Supporting References

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6. Key Words

Hyperammonaemia, acute encephalopathy, neuroprotection, Inborn errors of metabolism, CVVH, Inherited disorders of amino acid metabolism, Inherited disorders of organic acid metabolism, ammonia scavenger, Sodium benzoate, Sodium phenylbutyrate, Arginine, Carnitine, Caglumic acid.

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) A Siddique J Vujcikova – Consultant J Forster - Consultant	**Executive Lead** **Chief Medical Officer**
Details of Changes made during review: Minor formatting changes Section 2.2 revised and updated : - Rationale for stopping oral intake included - Rationale for treating hypoglycaemia added - 'Repeat if needed' deleted from consider fluid bolus (point 4) and replaced with 'If peripheral circulation is poor or child clinically shocked, further resuscitation with volume and/or inotropic support is needed'. Appendix 1 - Hyperammonaemia investigations and management flow chart revised and updated Hyperlinks updated	

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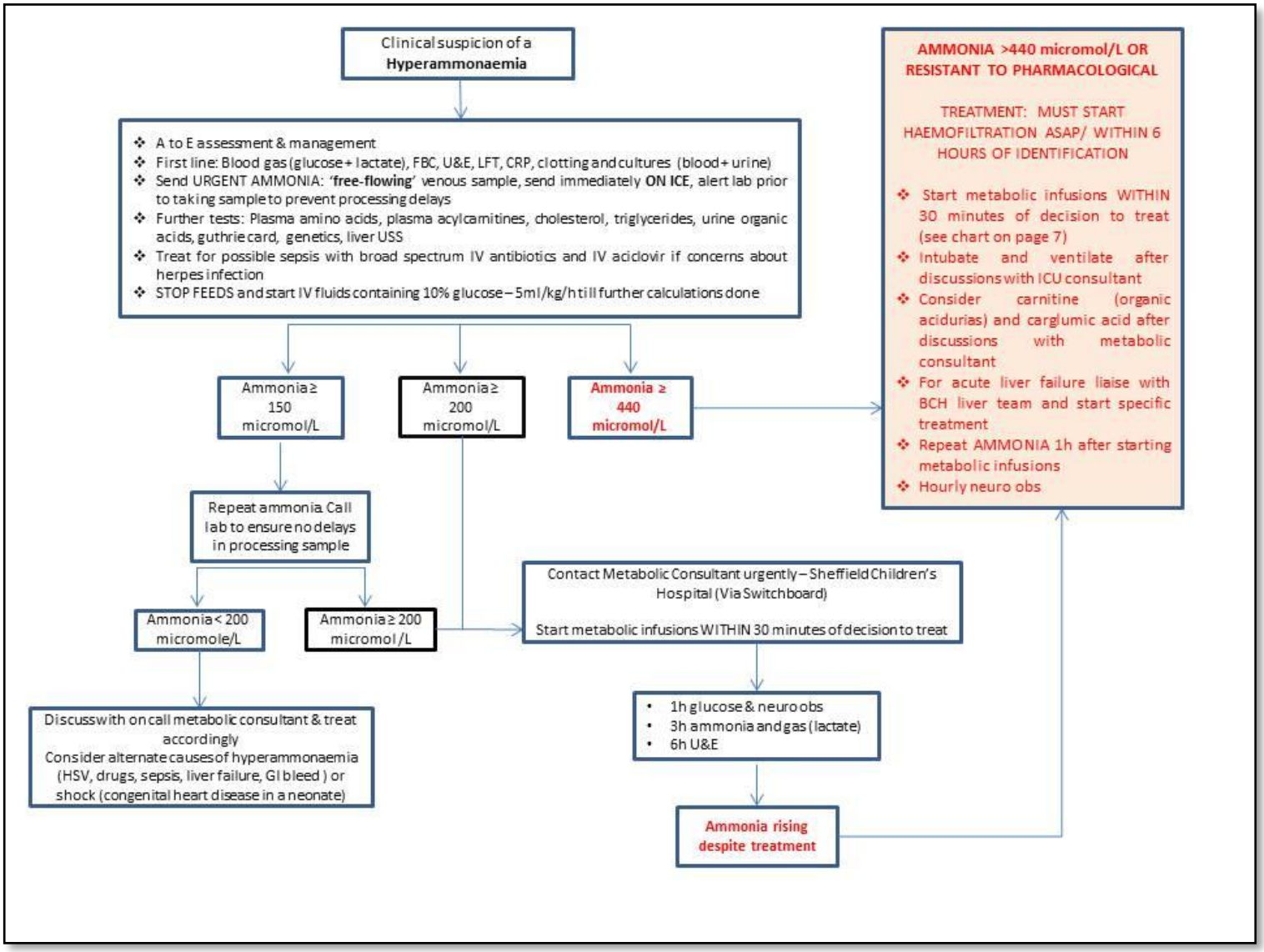
Hyperammonaemia investigations and management flow chart

HYPERAMMONAEMIA IS A TIME CRITICAL METABOLIC EMERGENCY WITH THE RISK OF DEATH OR SERIOUS BRAIN INJURY



Metabolic team: Sheffield Children's Hospital offers us 24h advice service (contact number: switchboard tel: 011420271207000)

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Birmingham Childrens Hospital - Metabolic Team (01213339999)