Investigation of Hyperammonaemia in Children and Adults

This document is intended to give guidance about the causes of hyperammonaemia in infants, children and adults, how to recognise it, and the basic principles of investigation and treatment.

Severe hyperammonaemia is a metabolic emergency.

Early recognition and intensive treatment may prevent a disastrous neurological outcome.

You should measure plasma ammonia in anyone who presents with altered consciousness or coma unless the cause of the altered consciousness or coma is injury, epilepsy or other recognised encephalopathy.

- In infants there will be drowsiness, irritability and vomiting, and there may be abnormalities of tone and posture with abnormal cycling movements.
- In adults there may be aggressiveness and confusion or ataxia.
- The presence of focal signs does not rule out hyperammonaemic encephalopathy: hemiplegia or sudden visual loss may be presenting symptoms and are likely to resolve if therapy is prompt.
- The presence of a respiratory alkalosis should prompt the measurement of ammonia.

Every unit which deals with acutely ill children or adults should have the facility to measure blood ammonia urgently. Samples should be sent to the lab immediately, ideally within 30 minutes of collection. Results will need to be obtained quickly to allow swift action to be taken and it is recommended to phone the lab before sending a sample.

Normal Plasma Ammonia Reference Limits:

Premature infants:	<150 umol/L
Neonates (<4 weeks):	< 100 umol/L
Infants >4 weeks and adults:	<80 umol/ L

In **children**, ammonia levels over 200 umol/l are highly suggestive of an **inherited metabolic disorder** (and may reach 1500-5000umol/l in urea cycle disorders) and require an **urgent repeat sample**.

Please note that **adults** may be significantly unwell with only slightly elevated ammonia levels.

All significantly elevated ammonia results should be confirmed urgently with a repeat sample.

If you identify severe hyperammonaemia you should **contact the on-call specialist metabolic paediatrician** to discuss the appropriate next steps. Very high ammonia will require haemodiafiltration or haemodialysis. Haemodialysis for children is available only at the Royal Hospital for Children in Glasgow.

Causes of Hyperammonaemia in Neonates

- Inherited disorders of the Urea Cycle
- Organic Acidaemias
- "Transient Hyperammonaemia of the Newborn" – only in premature infants who have an open ductus venosus
- Perinatal asphyxia
- Intravenous feeding and excessive protein intake
- Ill preterm neonates
- Neonatal Herpes simplex infection

Causes of Hyperammonaemia in Infancy and Childhood

- Inherited disorders of the Urea Cycle
- Other inherited disorders of ammonia metabolism
- Organic Acidaemias
- Advanced liver disease (including Cystic Fibrosis)
- Idiosyncrasy to Valproate
- Infection with urea-splitting organisms (esp Proteus) in an obstructed or atonic urinary tract
- Reye syndrome

Causes of Hyperammonaemia in Adulthood

- Inherited metabolic disorders, especially disorders of the urea cycle, may present at any age.
- Liver disease, especially with cirrhosis and abnormal porto-systemic blood flow
- Multi-organ failure
- In states of malnutrition, after bariatric surgery and in bacterial overgrowth within blind loops of bowel
- Infection with urea-splitting organisms (esp Proteus) in an obstructed or atonic urinary tract

Initial Biochemical Investigations	
Blood	• Ammonia • Full blood count • Glucose • Urea and electrolytes • Liver Transaminases • Creatine kinase • Lactate • Capillary blood gases • Amino acids • Bloodspots for acylcarnitines
Urine	• Ward test for acetoacetate ("ketones") • Freeze a specimen for organic acids and orotic acid

Initial Results	"Best guess" Diagnosis
Hyperammonaemia alone	Urea cycle disorder, OTC deficiency the most common
Hyperammonaemia + severe acidosis with or without hypoglycaemia	Organic acidaemia, especially propionic acidaemia
Hyperammonaemia + hypoglycaemia, usually not severely acidotic	Fatty acid oxidation disorder, Reye syndrome

General Aspects of Care and Nutrition

1. Discuss the case with the on-call metabolic consultant to agree the appropriate treatment plan. For patients known to have a particular disorder there may be appropriate drug therapies which have deliberately not been discussed in this short document as they may carry a risk of toxic side-effects.

2. Treat dehydration, acidosis or sepsis.

3. Temporarily stop all dietary protein including infant formula, and parenteral nutrition fluid containing amino acids. This must be reviewed after no more than 48 hours. Pay proper attention to the state of nutrition and avoid starvation: otherwise catabolism will cause hyperammonaemia to persist.

4. Initially give a generous carbohydrate energy intake as 10-15% glucose intravenously. Intralipid may be given to increase the energy intake, especially in the neonate, but you must exclude a fatty acid oxidation disorder first. Vomiting or impaired consciousness or airway instability may preclude enteral feeding. Use an oral solution of glucose polymer in boluses (NG or oral) or as a continuous NG feed if the enteral route can be used safely.

5. Watch continuously for signs of rising intracranial pressure, such as increasing confusion, increasing depth of coma, hypertension and slow heart rate.

6. If you are arranging a transfer to another hospital it is advisable for anyone with hyperammonaemia and any suspicion of raised intracranial pressure to be intubated for the journey. This should be discussed with the on-call metabolic consultant.

Original author: Dr Peter Robinson, IMD Scotland Protocols Subgroup.
Original publication: December 2017. Date for revision: December 2020.