BIMDG
British Inherited Metabolic Disease Group

UNDIAGNOSED HYPERAMMONAEMIA
DIAGNOSIS AND IMMEDIATE MANAGEMENT

Plasma ammonia concentrations are often a cause for concern and treatment may be very urgent. The symptoms are highly variable. Neonates often have an overwhelming illness, although respiratory alkalosis is an early sign. In infants the symptoms are more often 'gastro-intestinal' such as vomiting and anorexia combined with slow developmental progress. In older children neurological symptoms usually predominate with episodes of encephalopathy, often combined with slow developmental progress.

1. Interpretation

The interpretation of plasma ammonia values can be difficult and should always be done in conjunction with the history.

Normal values should be less than 50 μmol/l but mildly raised values are common – up to 80 μmol/l. Artifactually 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 be not be used. Values up to 80 μmol/l are common in patients with urea cycle disorders, even those with good metabolic control. Plasma ammonia concentrations are usually >100 μmol/l during an episode of decompensation but, on rare occasions, they may not be raised in the early stages. In neonates any illness may be responsible for values up to180 μmol/l. In any patient values in excess of 200 μmol/l require urgent attention. In all cases the history is important. The symptoms, signs, and treatment may all provide clues. There is no simple test that will indicate a diagnosis, such as blood gases. Organic acidaemias may present with respiratory alkalosis and urea cycle disorders with acidosis.

2. Investigations

- **Repeat plasma ammonia immediately if >150 μmol/l in children, >200 μmol/l in neonates**

- Plasma urea & electrolytes, liver function tests, clotting studies
- Blood glucose (plus hypoglycaemia 'screen' if blood glucose < 2.6 mmol/l – for protocol for undiagnosed hypoglycaemia – click here)
- Plasma amino acids (this should be done urgently if there is significant hyperammonaemia and a urea cycle disorder is suspected)
- Blood spot acyl carnitine profile ---- Continued on next page
- Blood pH and gases
- Blood Lactate

- Blood culture

- Urine amino acids (for transport defects – see below)
- Urine organic acids including urine orotic acid

For differential diagnosis - section 4. below

3. MANAGEMENT DO NOT DELAY.

- **Contact metabolic centre for advice regarding management and potential transfer**

Treatment of undiagnosed hyperammonaemia is urgent although the precise details are controversial because of concerns that the treatment may be potentially harmful. However the outcome of severe hyperammonaemia is frequently poor so the BIMDG supports an intensive approach. For further help with the diagnosis and management please consult your specialist centre.

Initial plan.

⇨ If the repeat plasma ammonia is > 250 μmol/l, arrange transfer to specialist centre *as soon as possible* but whilst waiting for transfer start treatment - see below. DO NOT DELAY.
⇨ For post-neonatal patients admitted to metabolic/general ward make a careful clinical assessment including blood pressure and even if the patient does not appear encephalopathic enter a Glasgow coma score (for details click here) This is very important since should the child deteriorate particularly around the time of a change of shifts, the new team will recognise any change.

The results of the blood tests are urgent so contact the laboratory to discuss them.

Management
Management decisions should be based mainly on the **clinical** status. It is particularly important to note any degree of encephalopathy.

All children with hyperammonaemia should have intravenous therapy and stop oral feeds until diagnosis known and patient is stable.

- Give Glucose 200 mg/kg **at once** (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes.
- Give normal saline 10 ml/kg unless the peripheral circulation is poor or the patient is frankly shocked, then give 20 ml/kg normal saline as a bolus immediately after the glucose. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
- Continue with glucose 10% at 5 ml/kg/h until next solution ready. – see below
- Quickly calculate the deficit and maintenance and prepare the intravenous fluids
    - Deficit: estimate from clinical signs if no recent weight available

- Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.

  It is assumed that the patient will be given sodium benzoate and sodium phenylbutyrate at full dose therefore use 10% glucose. If not giving full doses, use 0.18% Saline and 10% glucose (for instructions to make this solution click here).

- Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
- Recheck the electrolytes every 24 hours if still on intravenous fluids.

Medication: The medicines should be given as soon as possible as continuous intravenous infusions. Sodium benzoate and sodium phenylbutyrate can be given together: the maximum concentration for infusion being no more than 2.5 gram of each drug to 50ml of 5 or 10% dextrose. For more information about the medication please click here.

In an emergency the loading dose should be given initially followed by the maintenance dose.

Drug	**Loading dose over 90 minutes**	**Followed by maintenance dose over 24 hours**	**Maximum daily dose (every 24 hours thereafter)**	**Sodium content of daily maintenance dose**
Sodium benzoate	250 mg/kg	250 mg/kg	500 mg/kg	3.5 mmol/kg/d
Sodium phenylbutyrate	250 mg/kg	250 mg/kg	600 mg/kg	2.8 mmol/kg/d
Arginine	150 mg/kg	300 mg/kg	500 mg/kg	nil
Carnitine * See important note below	100 mg/kg	100 mg/kg	300 mg/kg	nil

IMPORTANT NOTE: 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.

After the initial treatment, it is strongly recommended that the doses are discussed with the regional metabolic centre. Use the BIMDG calculator (click here) for volumes and rates of infusions

- Consider giving a single oral dose of N-carbamyl glutamate (250 mg/kg). This is the treatment of choice for N-acetylglutamate synthase deficiency (very rare). It may also be of benefit for hyperammonaemia secondary to organic acidaemias.

- 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.

- Hyperglycaemia can be a problem. If the blood glucose exceeds 14 mmol/l and there is glycosuria, start an insulin infusion according to the local diabetic protocol rather than reducing the glucose intake.

-Potassium. Hypokalaemia is common so plasma potassium concentration should be monitored carefully. Potassium should be added once urine flow is normal and the plasma potassium concentration is known.

Continuation

Check the plasma ammonia after 3 hours,

a. If plasma ammonia is higher, arrange urgent transfer to metabolic centre for specialist management including haemofiltration.

b. If plasma ammonia is the same or lower, continue with the treatment and get the results of the tests as quickly as possible.

4. Differential diagnosis: Disorders associated with Hyperammonaemia

Inherited disorders: Urea cycle enzyme defects

- Carbamyl phosphate synthetase deficiency (CPS def)
- Ornithine carbamyl transferase deficiency (OTC or OCT def)
- Argininosuccinate synthetase deficiency (Citrullinaemia, ASS def)
- Argininosuccinate lyase deficiency (Arginosuccinic aciduria, ASA or ASL def))
- Arginase deficiency
- N-acetylglutamate synthetase deficiency (NAGS def)

Transport defects of urea cycle intermediates

- Lysinuric protein intolerance (LPI)
- Hyperammonaemia- hyperornithinaemia-homocitrullinuria syndrome (HHH syndrome)
- Citrin deficiency (citrullinaemia type II)

Organic acidurias

- Propionic acidaemia
- Methylmalonic acidaemia
- Isovaleric acidaemia and other organic acidaemias

Miscellaneous inherited disorders
Many metabolic disorders may cause mild- moderate hyperammonaemia.
Fatty acid oxidation disorders, congenital lactic acidoses (including pyruvate carboxylase deficiency) and hyperinsulinism- hyperammonaemia (HI-HA - increased glutamate dehydrogenase activity) can all cause hyperammonaemia, although other features usually predominate (e.g. hypoglycaemia) and severe hyperammonaemia is unusual.

Acquired disorders.

- Transient hyperammonaemia of the newborn (usually severe hyperammonaemia)
- 'Reyes' syndrome. (This is an acute metabolic encephalopathy and if this diagnosis is considered rule out inborn errors.)
- Liver failure from any cause, both acute and chronic
- Valproate therapy
- Infection with urease positive bacteria (particularly associated with stasis in the urinary tract)
- Leukaemia therapy including treatment with asparaginase
- Any severe systemic illness particularly in neonates
- Systemic herpes simplex in neonates (often severe hyperammonaemia)

The underlying aetiology will be apparent in the majority of cases following with test listed above. Confirmation is by molecular genetics or enzyme analysis. A skin or liver biopsy may be needed.

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