British Inherited Metabolic Disease Group

This protocol has 5 pages

HYPERAMMONAEMIA: UREA CYCLE DISORDERS OTC AND CPS DEFICIENCIES

IMMEDIATE ACTION

- **Triage to high priority**
- **The major complications are hyperammonaemia and encephalopathy. Meticulous treatment is very important as there is a high risk of neurological complications including cerebral oedema.**
- **Management should be based upon clinical status as per Section 2.**
- **Run IV 10% Dextrose/0.45% Sodium Chloride at 5ml/kg/hr ONLY until fluids can be accurately calculated**
- **These guidelines cover the first 24hr of management only – ongoing management should be guided by the child's specialist metabolic team. Inform them EARLY about the child**

1. Background & Signs of Decompensation

- The urea cycle converts ammonia into urea and defects of all the steps are now well documented. The clinical manifestations occur due to hyperammonaemia, albeit to varying degrees, associated with other metabolic disturbances. At a very early stage the plasma ammonia concentration may not be raised, probably because there is accumulation of glutamine in the brain before ammonia increases in the blood.
- Infections, fasting, diarrhoea or vomiting and any protein loading can lead to serious illness, with encephalopathy and even sudden death but an obvious precipitant is not always obvious.
- The early signs of decompensation may be subtle e.g. lethargy, loss of appetite or an exacerbation of pre-exiting neurological problems (irritability, fits, etc). Vomiting is common and should always be taken seriously.
- Treatment aims to reduce the production of ammonia: preventing catabolism by providing energy in the form of glucose - enterally or intravenously, and using medicines that promote the removal of nitrogen by alternative pathways. (see section 2)
- All these disorders may cause severe neurological complications and treatment of acute illness is urgent. The major complication of these disorders is cerebral oedema.

2.Management in hospital

- If the child is shocked or clearly very ill consider admission to ITU/High dependency.
- If admitted to a metabolic/general ward careful clinical assessment is essential including regular PEWS and neurological observations even if the patient does not appear encephalopathic.

The following blood tests should be considered: pH and gases

Ammonia (urgent)
Urea & electrolytes
Glucose (laboratory and bedside strip test)
Full blood count
Aminoacids (quantitative)
Blood culture

Consider other tests as clinically indicated.

Management decisions should be based primarily on the **clinical** status. The first decision about therapy is whether the child can be treated orally or will need intravenous therapy. Intravenous fluids are indicated if:

1. the child is unable to tolerate oral fluids, or
2. there is moderate or severe clinical dehydration

- **If there is any doubt at all, put up an intravenous line.**
- Treat any infection and constipation

A. ORAL. If the child is relatively well and not vomiting, oral feeds may be given. For young children (typically under 2 years) or those who already have enteral feeding tubes, the emergency feed can be given via such tubes.

FULL ENTERAL EMERGENCY FEED – glucose polymer solution

Use patient's own ER recipe wherever possible.

If not available then click here for age-based ER recipes.

If ER products not available use IV guidelines.

Oral rehydration solutions are low in CHO and not suitable

EMERGENCY FEED ADMINISTRATION

- Give feeding volume for body weight (see recipe)
- Feed orally: 2 hourly day and night
- If not tolerated or fluid requirements not met, administer continuously by tube, without delay
- Administer bolus or continuously by tube feed, without delay for a maximum of 24-36hours
- Introduce usual diet/feeds as soon as clinically stable

Medications

- Antipyretics: as clinically indicated
- If nausea/vomiting is a problem, antiemetics such as ondansetron may be helpful.
- Give the child's usual oral ammonia scavenging drugs if not vomiting. In an emergency these should be an increase from those used routinely and may be divided into 2 hourly doses to reduce the risk of vomiting.

Drug	Doses in ill patients*
Sodium benzoate	up to 500 mg/kg/day
Sodium phenylbutyrate	up to 500 mg/kg/day
Arginine	150 mg/kg/day

(For more information about the medicines click here). Seek specialist, help if uncertain about management.

Contact the child's specialist metabolic team and dietitian for further advice on the ER and introduction of usual diet/feeds

B. INTRAVENOUS. If the child is unwell and/or vomiting then IV treatment is needed:

IMMEDIATE FLUID RESUSCITATION:

- Give 0.9% sodium chloride 20 ml/kg as a bolus **if the peripheral circulation is poor or the patient is frankly shocked**. Repeat the sodium chloride bolus if the poor circulation persists as for a shocked non-metabolic patient.

INITIAL FLUIDS AFTER RESUSCITATION:

- Run IV fluids of Glucose 10%/Sodium Chloride 0.45% at 5ml/kg/h ONLY until accurate fluid rates have been calculated **– do not leave on this high rate longer than necessary**. (for instructions to make this solution click here).

FURTHER FLUID MANAGEMENT IN FIRST 24 HOURS:

- Ongoing fluid management in based upon administering the fluid deficit plus maintenance over 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).
- Deduct any fluid already given from the total for the first 24 hours.
- Potassium can be added once the plasma potassium concentration is known and the child is passing urine.
- Reassess hydration status and the need for ongoing IV fluids after 24 hours and if needed recheck the electrolytes every 24 hours.

MEDICATION: DO NOT DELAY STARTING MEDICATION.

- Sodium benzoate & phenylbutyrate should be given as continuous intravenous infusions, except in the mildest of cases (see above). In an emergency the doses given should always be an increase from those used routinely. In the short-term, arginine is less important than the others and an intravenous loading dose is not needed. (For more information about the medicines click here)
- **It has been proven safe to mix Sodium Benzoate, Sodium Phenylbutyrate and L-Arginine together in 10% glucose.** (maximum concentration 2.5g of each in 50mls or 25g in 500ml – *stability studies commissioned by BIMDG*). However if local guidelines state otherwise then they can be made in separate bags/syringes.

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	500 mg/kg	2.8 mmol/kg/d
Arginine	-	150 mg/kg	250 mg/kg	nil

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

*Note: Outside the UK Ammonul® may be used in place of sodium benzoate and sodium phenylbutyrate. This proprietary medicine is a mixture of sodium benzoate and sodium phenylacetate (For more information about the medicines click here)

- Treat any infection and constipation (which increases ammonia absorption from the gut).
- If nausea or vomiting is a problem ondasetron may be helpful.
- Hyperglycaemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol rather than reducing the glucose intake. **Strict supervision is essential.**
- 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.

3. Progress/Monitoring

If there is any hint of encephalopathy (lethargy, unusual behaviour, etc) start neurological observations - at least hourly - & seek specialist help. Under these circumstances, fluid volumes should be reduced and given via a central line as concentrated solutions to minimise the risk of cerebral oedema.

Reassess every 4-6 hours or earlier if there is any deterioration or no improvement. Clinical assessment should include PEWS and neurological observations.

- If deteriorating, seek specialist help without delay
- Blood tests should be repeated every 4-6 hours until stability is achieved
  Blood pH and gases
  Ammonia
  Urea & electrolytes

If improving continue, and for intravenous fluids and medicines see the previous section

If deteriorating (clinical state, hyperammonaemia), seek specialist help. Haemofiltration (or haemodialysis) may need to be considered urgently. Note peritoneal dialysis is less efficient. Exchange transfusion is dangerous and should not be used.

4. Re-introduction of enteral feeds:

As many more calories can be given enterally safely, enteral feeds should be introduced as early as possible. It is customary to delay the introduction of any protein or aminoacids but this will only prolong the period of catabolism. If necessary, consult your local dietitian for more details.

5. If not improving: If the child is not improving within 24-48hrs then it is essential that a specialist unit is contacted who may advise the use of Parenteral Nutrition or Essential Amino Acid supplementation to reduce the risk of ongoing catabolism from protein deficiency. Some degree of forward planning for this is advisable, for example over weekends/public holidays, and therefore ongoing close liaison with a specialist unit is strongly recommended.

6. Going Home: Only allow the child home if you and the family are entirely happy and you have discussed the problems with the consultant on call. The family must have a clear management plan and be prepared to return if the child deteriorates. Only allow the child home if you and the family are entirely happy. **It must be clearly demonstrated that the child can tolerate at least two successive feeds / meals before discharge.**

For further information please refer to:

Lichter-Konecki U, Caldovic L, Morizono H, et al. Ornithine Transcarbamylase Deficiency. 2013 Aug 29 [Updated 2016 Apr 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK154378/

Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. 2003 Apr 29 [Updated 2017 Jun 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1217/