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HYPERAMMONAEMIA: UREA CYCLE DISORDERS OTC AND CPS DEFICIENCIES

(standard version)

- **Please read carefully. Meticulous treatment is very important as there is a high risk of neurological complications including cerebral oedema.**

- **If the instructions do not make sense or a problem is not addressed you must discuss your concerns with the consultant on call.**

1. Background

The urea cycle converts ammonia into urea and defects of all the steps are now well documented. All cause hyperammonaemia, albeit to varying degrees, associated with other metabolic disturbances. All these disorders may cause severe neurological complications and treatment of acute illness is urgent. The disorders covered by this protocol are:

Carbamyl Phosphate synthetase deficiency (CPSD)
Ornithine transcarbamylase deficiency (OTCD)

Treatment is aimed at reducing the production of ammonia so the patients are treated with a low protein diet and medicines that promote the removal of nitrogen by alternative pathways.
Decompensation is often triggered by metabolic stress such as febrile illness, particularly gastro-enteritis, fasting and any protein loading but an obvious precipitant is not always apparent. The early signs of decompensation may be subtle - lethargy, loss of appetite or exacerbation of pre-exiting neurological problems (irritability, fits, etc). Vomiting is common and should always be taken seriously. However the signs may be difficult to assess such as just 'not right'. Always listen to parents carefully. They probably know much more than you do. Note that 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. The major complication of these disorders is cerebral oedema.

2. Admission

Almost all patients who present to hospital will require admission. 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 does not improve.

- **If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.**

3. Initial plan and management in hospital

⇨ If the child is shocked or clearly very ill arrange for admission to ITU.

⇨ If 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 following blood tests should be done:
- Blood pH and gases
- Ammonia (urgent)
- Urea & electrolytes
- Glucose (laboratory and bedside strip test)
- Full blood count
- Aminoacids (quantitative)
- Blood culture

4. Management

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

The first decision about therapy is whether the child can be treated orally or will need intravenous therapy.

- Factors that will influence the decision include, how ill is the child and whether they have deteriorated suddenly in the past?
- Can the child tolerate oral fluids?

If the child is relatively well - may be treated orally but assess very carefully.
If the child is obviously unwell - must be treated with intravenous fluids

If there is any doubt at all, put up an intravenous line.

A. ORAL If the child is relatively well and not vomiting oral feeds may be given

The emergency regimen should be used. This should be given either continuously if there is a risk of vomiting or as small boluses frequently. For more information about the emergency oral management click here

Age (years)	Glucose polymer concentration (g/100ml)*	Total daily volume**
0-1	10	150-200 ml/kg
1-2	15	95 ml/kg
2-6	20	1200-1500 ml
6-10	20	1500-2000 ml
>10	25	2000 ml

* If necessary, seek help from your local dietitian. In an emergency a heaped 5 ml medicine spoon holds approximately 7g of glucose polymer.

**For each drink the volume will generally be this figure divided by 12 and given 2 hourly.

Electrolytes; It is rarely necessary to add sodium since large amounts are given with the drugs (see below- 1g sodium benzoate & phenylbutyrate contain 7 mmol Na & 5.4 mmol Na respectively).However patients may need additional potassium supplements.

Medicines: The patient must also be given medicines, sodium benzoate, sodium phenylbutyrate and arginine. In an emergency the doses given should always be an increase from those used routinely. These should be divided into 2 hourly doses to reduce the risk of vomiting. (For more information about the medicines click here). Seek specialist, help if uncertain about management.

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

- 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.

B. INTRAVENOUS .

Most children will require intravenous therapy which should be started IMMEDIATELY.

- 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 5 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give up to 20 ml/kg normal saline instead of the 5 ml/kg.. 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: 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.

Arginine, Sodium Benzoate and Sodium Phenylbutyrate should be made up separately in 10% glucose. (maximum concentration 2.5g in 50mls) and given in a syringe pump piggy-backed (Y-

connector) into the main 10% glucose infusion as close to the entry site as possible. It is not advisable to add any of the medicines to the main infusion in case this has to be changed and then the quantity given may be uncertain as well as being wasteful. 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).

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	150 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.

- 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 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.

5. Progress:

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.

Monitoring Reassess after 4-6 hours of earlier if there is a change for the worse repeat the Clinical assessment which should include Glasgow coma score (click here) and blood pressure.
Blood tests

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.

6. **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 usual to give soluble glucose polymer initially 10% and increase this both volume and concentration as tolerated. 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.

7. 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.

For further information please refer to:

Saudubray J-M, van den Berghe G, Walter JH. (editors) Inborn Metabolic Diseases. Diagnosis and treatment. 5th Edition. Springer 2012

Last reviewed in Feb 2012