Contact Details Name: **Hospital** **Telephone:**

This protocol has 5 pages

HYPERAMMONAEMIA **due transport defects**

(standard version)

HHH **syndrome (hyperornithinaemia, hyperammonaemia, homocitrullinuria)**
LPI - **lysinuric protein intolerance**

- **Please read carefully. Meticulous treatment is 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

These disorders may cause hyperammonaemia although acute decompensation is not common. Both are treated with low protein diet and citrulline. Occasionally additional medication is needed.

Decompensation is often triggered by metabolic stress such as febrile illness, particularly diarrhoea and vomiting, fasting and any protein loading but an obvious precipitating cause 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.

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:

pH and gases
Ammonia
Urea & electrolytes
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.

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Electrolytes: These may be needed if the child has gastro-enteritis or other fluid losses. If sodium benzoate and / or sodium phenylbutyrate are used it is rarely necessary to add sodium since large amounts are given with the medicines (see below- 1g sodium benzoate & phenylbutyrate contain 7 mmol sodium & 5.4 mmol sodium respectively). However patients may need additional potassium supplements.

Medicines:
If the plasma ammonia concentration is < 80 μmol/l citrulline should be given at 400 mg/kg/d. If the child is unwell and/or the plasma ammonia concentration is > 80 μmol/l use the higher dose – 700 mg/kg/d. The patient should be reviewed after 4 hours (or earlier if deteriorating clinically) and if the plasma ammonia has increased, give sodium benzoate and sodium phenylbutyrate.
(For more information about the medicines click here)

- Treat any infection and constipation (which increases ammonia absorption from the gut). The value of lactulose is unproven.

Drug	Emergency doses
Sodium benzoate	250 mg/kg/day
Citrulline	700 mg/kg/day

B. INTRAVENOUS.

If the child is unwell

- 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 as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 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.
    - Give 0.45% saline/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 IV fluids.

If the child is obviously dehydrated, vomiting and/or unwell

Potassium can be added, if appropriate, once urine flow is normal and the plasma potassium concentration is known.

- 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.**

- 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. Note patients with LPI have a particular problem with Varicella infections. Start aciclovir if any doubt.

Medicines: If the plasma ammonia concentration is < 80 μmol/l citrulline should be given at 400 mg/kg/d. If the child is unwell and/or the plasma ammonia concentration is > 80 μmol/l use the higher dose – 700 mg/kg/d. The patient should be reviewed after 4 hours (or less if deteriorating clinically) and if the plasma ammonia has increased, give sodium benzoate and sodium phenylbutyrate. (For more information about the medicines click here)

Sodium benzoate & phenylbutyrate should be given as continuous intravenous infusions. These drugs can be given together - the maximum concentration for infusion being no more than 1 gram of each drug to 50ml of 5 or 10% dextrose. An intravenous preparation of citrulline is generally not available. It should be given orally as a continuous slow infusion.

Drug	**Doses for patients that are unwell**	**Sodium content**
Sodium benzoate	up to 500 mg/kg/day	2.45 mmol/kg/d
Sodium phenylbutyrate	up to 500 mg/kg/day	2.8mmol/kg/d

WARNING. 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

5. Progress:

If there is any hint of incipient encephalopathy (lethargy, unusual behaviour, etc) start neurological observations - at least hourly -and 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 After 4-6 hours of earlier if there is a change for the worse repeat
Clinical assessment. Continue to record status carefully including Glasgow coma score (for details click here) and blood pressure.

Blood tests
- pH and gases
- Ammonia
- Urea & electrolytes,

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

If deteriorating (clinical state, acidosis, hyperammonaemia, fluid overload), seek specialist help. Haemofiltration (haemodialysis) may need to be considered. 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 as well as medication 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 also customary to delay the introduction of any protein or aminoacids but this will only prolong the period of catabolism so it is recommended that small quantities of protein or aminoacids are introduced at an early stage. 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

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