British Inherited Metabolic Disease Group

Contact Details Name:
Hospital
Telephone:

This protocol has 5 pages

HYPERAMMONAEMIA IN UREA CYCLE DISORDERS
NAGS DEFICIENCY

(N-Acetyl glutamate synthase deficiency)
(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 disorder covered by this protocol is:

N-Acetyl glutamate synthase (NAGS) deficiency

Treatment is aimed at reducing the production of ammonia so the patients are treated with N-carbamyl glutamate and sometimes 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 diarrhoea or vomiting, 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, most 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, which can be severe and of sudden onset.

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

Only if the child is relatively well and not vomiting and oral feeds may be given. **Most children will require intravenous therapy which should be started IMMEDIATELY.**

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 should be added to the drinks if vomiting and/or diarrhoea is a problem using standard rehydration mixtures following manufacturer's instructions but substituting glucose polymer solution for water.

Medicines: The patient **must** be given their medicines. If the patient is on regular N-carbamyl glutamate double the dose. If doses of N-carbamyl glutamate have been missed the patient should be given a single large dose of N-carbamylglutamate 200 mg/kg orally and then continue with double their normal dose. If the patient is on sodium benzoate and/or sodium phenylbutyrate these should be given again at double the normal dose for the patient.

- 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.

PROGRESS:

The patient's progress must be reviewed after 3 hours.

- If the plasma ammonia concentration is normal (<50 μmol/l) and the child is well without any vomiting, the patient can resume their usual treatment.

-If the plasma ammonia concentration is between 50 and 120 μmol/l and no vomiting nor encephalopathy, continue current oral therapy.

-If the plasma ammonia concentration is >120 μmol/l, the patient is vomiting or encephalopathic, start intravenous therapy AT ONCE.

B. **INTRAVENOUS** .

If there is any doubt about management start intravenous therapy.

- 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 **ONLY until next solution is ready– do not leave on this high rate longer than necessary**. – 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.
  - If the patient is likely to be given sodium benzoate and sodium phenylbutyrate at full dose use 10% glucose in view of the sodium load. If not giving full doses, use 0.18% Saline and 10% glucose (for instructions to make this solution click here).
  - If not giving the medicines use Glucose 10%/saline 0.45% (for instructions to make this solution click here).
  - Having calculated the deficit and the maintenance, administer the appropriate rate of 0.45% saline/10% glucose (or alternative fluid) to correct the deficit within 24 hours
- Recheck the electrolytes every 24 hours if still on intravenous fluids.

Medication: There is no intravenous preparation of N-carbamyl glutamate. If at all possible continue to give it enterally, if necessary by slow continuous infusion through a naso-gastric tube. If the patient is on regular N-carbamyl glutamate double the dose. If doses of N-carbamyl glutamate have been missed the patient should be given a single large dose of N-carbamylglutamate 200 mg/kg enterally and then continue with double their normal dose.

Initial Plan

- If the child is relatively well with a GCS of >10 assess the response both clinical and biochemical (plasma ammonia) in 3 hours.

- If the child is encephalopathic (GCS<10), vomiting or plasma ammonia concentration is greater than 150 μmol/l start treatment at once with intravenous sodium benzoate, sodium phenylbutyrate and arginine (For more information about the medicines click here) as well as N-carbamylglutamate.

Arginine, Sodium Benzoate and Sodium Phenylbutyrate should be made up separately in 10% glucose. (maximum concentration 2.5g in 50mls or 25g in 500ml) and given via a syringe pump or infusion pump piggy-backed (Y- connector) into the main 10% glucose infusion as close to the entry site as possible. The medicines should be made up in separate syringes or bags. For patients over 40 kg use the adult protocol. In the short-term, arginine is less important than the others and an intravenous loading dose is not needed.

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 22.5 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

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)

After the initial treatment, it is strongly recommended that the doses are discussed with the regional metabolic centre.

On reassessment

The patient's progress must be reviewed after 3 hours.

- If the plasma ammonia concentration is normal (<50 μmol/l) and the child is well (GCS>12) without any nausea or vomiting, the patient can resume oral treatment.

-If the plasma ammonia concentration is between 50 and 120 μmol/l and GCS>10 continue current intravenous therapy.

-If the plasma ammonia concentration is >120 μmol/l, the patient is deteriorating (GCS<10) continue intravenous therapy and seek specialist help urgently.

- 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 at least 4-6 hours or earlier if there is a change for the worse repeat the Clinical assessment which should include Glasgow coma score (for details 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, Baumgartner MR, Walter JH. (editors) Inborn Metabolic Diseases. Diagnosis and treatment. 6th Edition. Springer 2016