BIMDG
British Inherited Metabolic Disease Group

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This protocol has 6 pages

MANAGEMENT OF A BABY AT RISK OF A UREA CYCLE DISORDER AT BIRTH

1. Is the diagnosis of the fetus already known for certain?

If yes go to 2.
If not, go to 3.

2. When did the sibling (or relative) become ill?

- **If the previous relative became ill in the neonatal period,** **go to section A on page 3**
- **If the previous relative became ill after the neonatal period** **go to section B on page 5**
- **If uncertain, use section A.**

If the diagnosis is not known proceed to 3.

3. A careful history is essential and should be reviewed by a specialist. In particular when did the previous child become ill, in the neonatal period or later? Is the likely diagnosis known? Work out the quickest way to establish the diagnosis. Seek specialist help if necessary.

4. If a previous sibling became ill shortly after birth, discuss management with specialist.

- Consider prenatal testing at a late stage if possible. This will facilitate management of the new baby if this was not done at an earlier stage in pregnancy.
- Consider transferring the mother before birth to a centre with all facilities for managing an affected baby.
- Consider delivering the baby by Caesarean section as this minimizes the metabolic stress of birth and the timing of the delivery is known.
- Consider giving sodium benzoate to the mother from 38 weeks gestation to make the management easier. This is experimental but appears to work well. The nature of this treatment must be explained (Das et al 2008).

5. The pregnancy should proceed normally. In the third trimester obtain supplies of the medicines used in urea cycle disorders – sodium benzoate, sodium phenylbutyrate and arginine – oral and intravenous (and N-carbamyl glutamate if NAGS deficiency is a possibility).

6. Inform the clinical biochemistry laboratory about the impending birth, as it is essential that results are available quickly.

At this stage the management will depend on the illness in the previous sibling.

- **If the previous relative became ill in the neonatal period,** **go to section A on page 3**
- **If the previous relative became ill after the neonatal period** **go to section B on page 5**

Important note: Whilst females with OTC deficiency usually have mild disease some with unfavourable lyonisation will have severe disease. As it is not possible to predict the phenotype, females with a severe mutation should be managed as directed in section A until the phenotype is obvious.

SECTION A

IF THE PREVIOUS SIBLING BECAME ILL IN THE NEONATAL PERIOD:

A1. Immediately after birth, transfer the baby to the neonatal unit and start an intravenous infusion of 10% glucose at 4 ml/kg/hr (glucose 6.6 mg/kg/min). It is important to have this infusion running within 30 minutes of birth. This is to prevent the normal fall in blood glucose that triggers activation of catabolic pathways in the baby. (Subsequently the glucose infusion may be reduced to avoid fluid overload.)

A2. If the baby remains well, at 4 hours offer a milk feed (breast or infant formula). Then give:

- Sodium benzoate 50 mg/kg and
- L-arginine solution 100mg/kg orally.
- Continue the same dose 6 hourly until the diagnosis is known or a change is advised.

A3. At 6 hours of age measure plasma ammonia.

⇨**If the plasma ammonia < 80 μmol/l**:

- repeat in 6 hours and if it stays at this concentration, monitor at 6 hourly intervals
- continue to offer milk feeds approximately 4 hourly
- stop the intravenous dextrose infusion if ammonia remains <80 μmol/l at 24 hrs of age

⇨**If the plasma ammonia 80 – 150 μmol/l**:

- repeat in 4 hours and if it stays at this concentration, monitor at 6 hourly intervals
- stop feeds and continue intravenous dextrose infusion

⇨**If ammonia > 150 μmol/l** or if the baby becomes unwell:

- **repeat immediately, stop feeds and contact the specialist centre** without waiting for the result of the repeat plasma ammonia.

A4. In addition to the plasma ammonia, measure the plasma aminoacids (quantitatively) urgently at approximately 12 hours of age regardless of the plasma ammonia concentration

A5. If the ammonia exceeds about 150 μmol/l, depending on the time course, the specialist centre will probably recommend:

- Stopping feeds
- Increasing the intravenous infusion of 10% glucose
- Giving medicines; sodium benzoate, sodium phenylbutyrate and arginine intravenously
- Monitoring plasma ammonia concentrations at least 4 hourly.

Details of medicines:
For OTC and CPS deficiencies give sodium benzoate and sodium phenylbutyrate each at 250 mg/kg over 90 minutes. Following this, give 250 mg/kg/24 hours of each drug, together with arginine 150mg/kg/24 hours.

For citrullinaemia and argininosuccinic aciduria give arginine 300 mg/kg and sodium benzoate 250 mg/kg over the first 90 minutes. Following this, give arginine 300 mg/kg/day and sodium benzoate 250 mg/kg/day.

For NAGS deficiency give a single dose of N-carbamylglutamate 250 mg/kg through a naso-gastric tube.

If the diagnosis is uncertain, treat as OTC deficiency. A single oral dose of N-carbamylglutamate 250 mg/kg may be given.

More information may be found in emergency protocols for urea cycle disorders on the BIMDG website. For further information about the medicines click here . **Use the calculator** (click this link) **for volumes and rates of infusions.**

A6. If the plasma ammonia >150 μmol/l monitor ammonia, U&E, bicarbonate & glucose 4-6 hrly.
If the ammonia is >200 μmol/l, monitor it 3 hourly.
If it is >250 μmol/l, seek specialist advice at once. Haemofiltration is likely to be needed urgently.

A7. If hyperglycaemia is a problem (consistently > 8 mmol/l) do not reduce the glucose infusion. Infuse insulin, initially at 0.05 U/kg/hr, and adjust as necessary. **Strict supervision is essential.** Monitor blood glucose after 30 minutes and subsequently every hour, because some neonates are very sensitive to insulin.

A8. It is usually unnecessary to add sodium to the infusions in the first 24 hours because large amounts are given with the drugs (1g sodium benzoate & phenylbutyrate contain 7 mmol Na & 5.4 mmol Na respectively). It will, however, probably be appropriate to change the maintenance glucose infusion to one containing sodium and potassium after the first 24 hours and this may be necessary sooner. Arginine hydrochloride may lead to a mild hyperchloraemic acidosis. If metabolic acidosis is a problem, infuse sodium bicarbonate (**CARE!**).

A9. Unless the plasma ammonia concentration is still >200 μmol/l, some enteral feeds should be started within 48 hours of birth. Discuss the feed to use and the rate of introduction with the metabolic centre. If mother wishes to breast feed, she should express as she should be able to breast feed her baby, even if affected, once the metabolic state is stable.

A10. The drugs can be changed to oral preparations once feeds are tolerated.

Note: The treatment proposed may mask the biochemical changes of disease. Careful follow-up is essential.

SECTION B

IF THE PREVIOUS SIBLING BECAME ILL AFTER THE NEONATAL PERIOD:

B1. If the birth is complicated (birth asphyxia, etc) start a glucose infusion as soon as possible after birth. This is to prevent the normal fall in blood glucose that triggers catabolic pathways in the baby. Admission to SCBU for assessment is advisable. Complications may not only be responsible for symptoms that mimic those of hyperammonaemia but they also elevate plasma ammonia concentrations.

B2. If all proceeds normally, start milk feeds (breast or infant formula).

B3. At 24 hours of age measure plasma ammonia and aminoacids (quantitative). If the diagnosis is to be made by molecular genetics send blood sample. Cord blood should not be used because of the possibility of maternal contamination.

- If plasma ammonia < 60 μmol/l repeat in 24 hours.
- If plasma ammonia 60 – 150 μmol/l repeat in 12 hours
- If plasma ammonia > 150 μmol/l or if the baby becomes unwell **repeat immediately**

Early clinical signs of hyperammonaemia include tachypnoea/ respiratory alkalosis, alterations in tone or activity.

B4. Next stage:

- If plasma ammonia remains less than 80 μmol/l at 48 hours, continue to offer milk feeds and observe.

- If plasma ammonia is between 80 – 150 μmol/l and the baby appears well:
  - Repeat at 12 hourly intervals.
  - Try to get results of plasma aminoacids as soon as possible.
  - Change feeds to 10% soluble glucose polymer. For more information about these feeds click here

- If plasma ammonia is > 150 μmol/l and the baby appears well:
  - Repeat in 4 hours.
  - Discuss with specialist
  - Change feeds to 10% soluble glucose polymer. For more information about these feeds click here

- If repeat plasma ammonia exceeds 200 μmol/l and/or the child is unwell (refusing to feed, tachypnoeic, drowsy, floppy, vomiting, etc)
  - Repeat plasma ammonia at once.
  - **Follow instructions at A5 above.**

B5. If mother wishes to breast feed, she should express as she should be able to breast feed her baby, even if affected, once the metabolic state is stable.

B6. Get the results but note that the treatment proposed may mask the biochemical changes of disease. Careful follow-up is essential.

Reference: Das AM, Illsinger S, Hartmann H, Oehler K, Bohnhorst B, Kuehn-Velten N, Luecke T. Prenatal Benzoate Treatment in Urea Cycle Defects. Arch Dis Child Fetal Neonatal Ed. 2008 Nov 13. [Epub ahead of print]

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