



# BIMDG

British Inherited Metabolic Disease Group

PATIENT NAME

HOSPITAL

DATE OF BIRTH

EMERGENCY CONTACT

0900-1700 Monday to Friday  
Out of hours

## ADULT EMERGENCY MANAGEMENT UREA CYCLE DEFECTS, INCLUDING:

1. OTC (ornithine transcarbamylase) deficiency
2. CPS1 (carbamylphosphate synthase 1) deficiency
3. citrullinaemia (argininosuccinate synthase deficiency)
4. argininosuccinic aciduria (argininosuccinate lyase deficiency)
5. arginase deficiency
6. NAGS (N-acetylglutamate) deficiency

### IMMEDIATE ACTIONS

Triage to high priority

Maintain glucose 6-10 mmol/L.

**These guidelines are intended for immediate emergency management only. Please contact your local metabolic team early for specific advice on individual patients.**

### BACKGROUND

The urea cycle converts ammonia into urea and defects of all the steps are well documented. Metabolic decompensation is associated with **hyperammonemia**, potentially leading to life threatening encephalopathy. Decompensation is often triggered by metabolic stress such as intercurrent illness, fasting, diarrhoea or vomiting, but an obvious precipitant is not always apparent. Patients presenting to A&E **must be treated seriously**, especially if they are vomiting or have impaired consciousness. Early intervention is essential to prevent cerebral oedema becoming established and irreversible.

Treatment is aimed at reducing the production of ammonia so patients are treated with a low protein diet and medicines that promote the removal of nitrogen by alternative pathways.

### **SIGNS OF DECOMPENSATION**

The early signs of decompensation may be subtle - **lethargy, loss of appetite, change in behaviour or exacerbation of pre-existing 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 patients and their carers carefully. Their assessment of the conscious level and precipitating factors should be taken into account.

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**.

**If there is any doubt at all, the patient should be admitted, even if only for a short period of observation.**

### **INITIAL ASSESSMENT AND MANAGEMENT IN HOSPITAL**

If the patient is shocked or clearly very ill arrange for admission to ITU / HDU.

Management decisions should be based primarily on the **clinical** status. It is particularly important to note any degree of encephalopathy. If the patient is relatively well – they may be treated orally using their [oral emergency regimen \(click here\)](#) (generally give 200ml of a 25% glucose polymer (eg Maxijul) solution every 2 hours) but assess very carefully. If the patient is obviously unwell – they must be treated with intravenous fluids.

Record the [Glasgow Coma Scale \(click here\)](#). This will allow early identification of encephalopathy and deterioration.

### **INITIAL INVESTIGATIONS**

Blood pH and gases

Ammonia – send to lab urgently on ice and contact the lab to let them know to expect it

Urea & electrolytes

Glucose

Full blood count

Amino acids (quantitative)

Other tests as indicated by the clinical findings (eg. CRP, blood and urine cultures)

### **TREATMENT**

1. Correct dehydration initially with 0.9% NaCl.

2. Natural protein intake should be stopped and intravenous 10% dextrose started as soon as possible at a rate of 2mls/kg/hr. (e.g. 140 mls/hr in a 70 kg person).

3. If there is clinical suspicion of hyperammonaemia or the plasma ammonia level is significantly elevated commence intravenous treatment as in appendix 1 (below). **Note: the different urea cycle defects require different doses and combinations of medications – please ensure you are following the correct guidance for the patient's specific condition.**

**Many hospital pharmacies may not stock sufficient quantities of these medications for the average adult patient. In this case if the patient is encephalopathic, resort to haemodialysis/filtration urgently. Some adult patients with known urea cycle defects will keep an emergency medication pack at home and will bring this with them to hospital.**

4. Treat any underlying infection or other clinical problem.
5. Give analgesia, anti-pyretic or an anti-emetic as required.
6. Consider the possibility of refeeding syndrome in susceptible patients.

## **MONITORING**

Reassess regularly and if there is a change for the worse repeat the clinical assessment which should include the [Glasgow Coma Scale \(click here\)](#) and blood tests:

**Blood pH & gases**

**Ammonia**

**Urea & electrolytes**

**Glucose:** Hyperglycaemia can occur. If the blood glucose exceeds 10 mmol/L, start an insulin infusion according to the local diabetic protocol rather than reducing the glucose intake. **Strict supervision is essential.** National guidelines are available at:

([http://www.diabetes.org.uk/About\\_us/Our\\_Views/Care\\_recommendations/The-Management-of-Diabetic-Ketoacidosis-in-Adults/](http://www.diabetes.org.uk/About_us/Our_Views/Care_recommendations/The-Management-of-Diabetic-Ketoacidosis-in-Adults/)).

**Potassium:** Potassium concentration should be monitored and corrected appropriately.

If signs of encephalopathy develop - seek specialist help. ITU support will be required. Haemofiltration (haemodialysis) may need to be considered urgently. Fluid volumes may need to be reduced and given via a central line as concentrated solutions to minimise the risk of cerebral oedema.

## **RE-INTRODUCTION OF ENTERAL FEEDING**

As the patient improves, oral or enteral feeds should be introduced as early as possible. Natural protein intake should be reintroduced / increased as tolerated. Anti-emetics may be needed. Consult your local metabolic dietitian or specialist centre for more details. See the BIMDG [oral emergency regimen \(click here\)](#) for UCD for more details.

## **MORE USEFUL INFORMATION**

<http://www.bimdg.org.uk/> and click on the red tab for emergency guidelines.

Genereviews: <http://www.ncbi.nlm.nih.gov/books/NBK1116/>

Pubmed: <http://www.ncbi.nlm.nih.gov/pubmed/>

## APPENDIX 1

### EMERGENCY INTRAVENOUS TREATMENT FOR UREA CYCLE DISORDERS

#### HOW TO MAKE UP THE INFUSION

**NOTE: THE FOLLOWING INSTRUCTIONS ARE FOR THE SPECIFIC CONCENTRATIONS OF MEDICATIONS AS LISTED BELOW – ALWAYS CHECK THE VIALS FIRST.**

**e.g. GIVEN THE PATIENT'S EMERGENCY IV PACK CONTAINS:**

L-Arginine @ 600 mg/mL **or** L-arginine @ 500mg/mL

Sodium benzoate @ 200 mg/mL

Sodium phenylbutyrate @ 200 mg/mL

These can all be mixed together in 10% dextrose as detailed below and given continuously at a rate of 2mls/kg/hour (replacing the infusion that was initially started). \* Occasionally fluid volumes may need to be reduced and given via a central line as concentrated solutions to minimise the risk of cerebral oedema. In this case the maximum concentration for infusion is 50mg/mL for sodium benzoate or sodium phenylbutyrate or 100mg/mL for arginine.

**An anti-emetic may also be given if needed: eg. ondansetron.**

**1. Guideline for OTC (ie. ornithine transcarbamylase) and CPS1 (carbamylphosphate synthase 1) deficiencies:**

L- arginine 100 mg/kg/day  
Sodium benzoate 250 mg/kg/day  
Sodium phenylbutyrate 250 mg/kg/day

#### **How to make up the infusion:**

To a 500 mL bag of 10% dextrose add:

- 1.75 mls of L-arginine (600mg/mL) solution **or** 2.1 mls of L-arginine (500mg/mL)
- 12.5 mls of sodium benzoate solution
- 12.5 mls of sodium phenylbutyrate solution

Run at the following rates according to weight:

|                 |    |     |     |     |     |
|-----------------|----|-----|-----|-----|-----|
| Weight (kg)     | 40 | 50  | 60  | 70  | 80  |
| Rate (mls/hour) | 80 | 100 | 120 | 140 | 160 |

**2. Guideline for citrullinaemia (ie. argininosuccinate synthase deficiency) and argininosuccinic aciduria (ie. argininosuccinate lyase deficiency):**

L- arginine 500 mg/kg/day  
Sodium benzoate 250 mg/kg/day  
Sodium phenylbutyrate 250 mg/kg/day

**How to make up the infusion:**

To a 500 mL bag of 10% dextrose add:

- 8.75 mls of L-arginine (600mg/mL) solution **or** 10.5 mls of L-arginine (500mg/mL)
- 12.5 mls of sodium benzoate solution
- 12.5 mls of sodium phenylbutyrate solution

Run at the following rates according to weight:

|                 |    |     |     |     |     |
|-----------------|----|-----|-----|-----|-----|
| Weight (kg)     | 40 | 50  | 60  | 70  | 80  |
| Rate (mls/hour) | 80 | 100 | 120 | 140 | 160 |

**3. Guideline for arginase deficiency:**

Sodium benzoate 250 mg/kg/day  
Sodium phenylbutyrate 250 mg/kg/day

**NOTE: NO ADDITIONAL ARGININE IS GIVEN.**

**How to make up the infusion:**

To a 500 mL bag of 10% dextrose add:

- 12.5 mls of sodium benzoate solution
- 12.5 mls of sodium phenylbutyrate solution

Run at the following rates according to weight:

|                 |    |     |     |     |     |
|-----------------|----|-----|-----|-----|-----|
| Weight (kg)     | 40 | 50  | 60  | 70  | 80  |
| Rate (mls/hour) | 80 | 100 | 120 | 140 | 160 |

#### 4. Guideline for N-acetylglutamate synthetase (NAGS) deficiency:

L- arginine 100 mg/kg/day  
Sodium benzoate 250 mg/kg/day  
Sodium phenylbutyrate 250 mg/kg/day

##### How to make up the infusion:

To a 500 mL bag of 10% dextrose add:

- 1.75 mls of L-arginine (600mg/mL) solution **or** 2.1 mls of L-arginine (500mg/mL)
- 12.5 mls of sodium benzoate solution
- 12.5 mls of sodium phenylbutyrate solution

Run at the following rates according to weight:

|                 |    |     |     |     |     |
|-----------------|----|-----|-----|-----|-----|
| Weight (kg)     | 40 | 50  | 60  | 70  | 80  |
| Rate (mls/hour) | 80 | 100 | 120 | 140 | 160 |

**Medications specific to NAGS deficiency:** Some patients may be treated with regular oral N-carbamyl glutamate (carglumic acid, Carbaglu®). 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 nasogastric tube.

##### Additional notes:

1. \*the guideline authors have administered the medications like this for many years without difficulty – however mixing of the 3 medications may not be in line with all hospital pharmacy policies. If needed, each medication can also be made up separately in 10% dextrose (maximum concentration 25g in 500ml) and given via an infusion pump piggy-backed (Y-connector) into the main 10% dextrose infusion as close to the entry site as possible.
2. It can sometimes take a little time to prepare the intravenous medications (sodium benzoate, arginine, sodium phenylbutyrate). Do not delay in starting the intravenous dextrose 10% or in giving anti-emetics if needed – start these first whilst you are organising the other medications.
3. In the obese patient it may be more appropriate to give medications based on body surface area rather than body weight – contact your metabolic team for further advice.
4. If needed additional calories can be given as eg. intralipid 20%.