orphanaesthesia

Anaesthesia recommendations for

Urea cycle disorders

Disease name: Urea Cycle Disorders

ICD 10: E72.2

Synonyms: Disorders of Urea cycle metabolism, UCDs, Hyperammonaemia

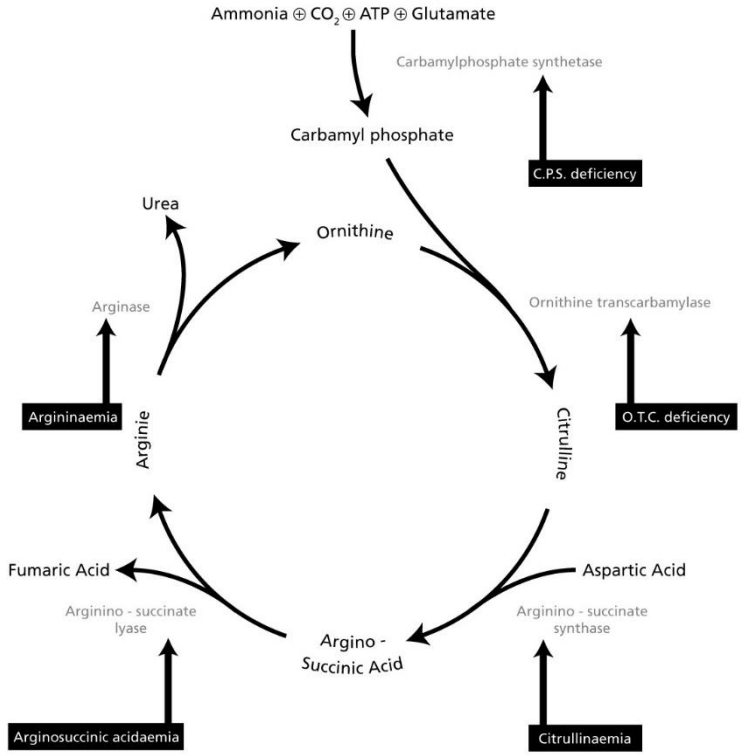
Disease name:	**N-acetylglutamate synthase deficiency** Synonyms: NAGS deficiency, NAGSD	ICD 10: E72.2
Disease name:	**Carbamylphosphate synthetase deficiency** Synonyms: CPS deficiency, CPS 1 deficiency, Carbamylphosphate synthetase 1 deficiency, CPS1D	ICD 10: E72.2
Disease name:	**Ornithine Transcarbamylase Deficiency** Synonyms: OTC deficiency, OTCD	ICD 10: E72.4
Disease name:	**Citrullinemia** Synonyms: Arginosuccinate Synthetase Deficiency, ASSD	ICD 10: E72.2
Disease name:	**Argininosuccinate lyase deficiency** Synonyms: Argininosuccinic aciduria, ASL deficiency, ASLD	ICD 10: E72.2
Disease name:	**Argininaemia** Synonyms: Arginase deficiency, Hyperargininemia, ARG1D	ICD 10: E72.2

Disease summary: The urea cycle is a series of reactions that occur in the liver whereby ammonia, the neurotoxic by-product of amino acid deamination, is converted to urea. Urea cycle disorders (UCDs) are inborn errors of ammonia detoxification and arginine synthesis caused by deficiencies in any one of the six enzymes or two transporters of the urea cycle pathway – see figure 1 [1,2,43]. There are 6 UCDs in total. Ornithine transcarbamylase deficiency (OTCD) the most common, is inherited as X-linked dominant. The remaining four are of autosomal recessive inheritance and include carbamoylphosphate synthetase-1 deficiency (CPS1D), argininosuccinate synthetase deificiency (ASSD/citrullinemia type 1), argininosuccinate lyase deficiency (ASLD), arginase-1 deficiency and N-acetylglutamate synthase deficiency (NAGSD).

The perioperative period is important for patients with UCDs because physiological and psychological stress can induce a catabolic state resulting in acute metabolic decompensation and a potentially fatal hyperammonaemia characterised by cerebral oedema and encephalopathy [2–4,43]. UCDs are the commonest inborn errors of hepatic metabolism with an incidence of 1:8,000 to 1:44,000 live births [2–5,44]. Disease prevalence is thought to

exceed current estimation due to the absence of reliable new-born screening and under-diagnosis of fatal cases. Multiple mutations have been recognised and some disorders such as OTCD have heterogenous penetrance and phenotypes, due to variability in gene activation and hepatocyte expression [1,2,8–15,43].

Protein is not stored within the body but exists in balance between anabolism and catabolism. Excess protein (from dietary intake or catabolic processes) is deaminated and these amino acids are then broken down to release nitrogen as ammonia. Excess ammonia has toxic effects particularly within the central nervous system. The urea cycle takes place primarily within the liver and converts ammonia into urea which is renally excreted. See figure 1:



Partial or complete absence of these mitochondrial enzymes impairs the conversion of ornithine and carbamylphosphate to urea and results in the accumulation of ammonia and, depending on the disorder in question, also citrulline (argininosuccinate synthetase deficiency), arginosuccinic acid (argininosuccinate lyase deficiency), fumaric acid (arginase 1 deficiency), glutamine (carbamoylphosphate synthetase 1 deficiency) or arginine (ornithine transcarbamylase deficiency) [6].

OTCD is the commonest of the five urea cycle defects (approximately 60% of UCD patients) followed by ASLD (approximately 16%) and ASSD/citrullinemia type 1 (approximately 14%) [6–8].

Severe neonatal forms of the disease (in OTCD: typically, hemizygous males) present in the first few days of life as “floppy infants” with hyperammonaemia, a respiratory alkalosis, hyperventilation, vomiting, irritability and lethargy which can progress to seizures, encephalopathy, coma and death [1–2,4–5,10,43]. Milder forms of the disease (in OTCD: more commonly, heterozygous females) present anytime from infancy to adulthood and can be triggered by illness, stress or other events associated with protein catabolism [1–2,8–15,43].

Complications of UCDs include developmental delay, intellectual disability and progressive liver damage. People with later onset UCDs may experience episodes of altered mental state

(e.g. delirium, erratic behaviour, reduced consciousness), headaches, vomiting, ataxia, aversion to protein foods, anorexia, abnormal GI function and seizures [1–2,7,43].

Liver transplantation is curative [2, 9–10,14,16–19,43]. Existing neurological damage cannot be corrected, making early treatment and avoidance of decompensation vital. Perioperative management aims to avoid metabolic decompensation by minimising physical and psychological stress; maintaining optimal hydration status; preventing protein catabolism; and facilitating nitrogen excretion [1–4,10,18,43].

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Typical surgery

Diagnostic procedures: lumbar puncture, liver biopsy, computerised tomography or magnetic resonance imaging.

Minor surgical procedures: vascular access devices, percutaneous gastrostomy, peritoneal dialysis catheters.

Major surgical procedures: liver transplantation.

Type of anaesthesia

Stress can precipitate a hyperammonemic crisis and acute decompensation [10]. It is therefore essential to deliver a patient-centred anaesthetic which minimises psychological stress, promotes anxiolysis and modulates the stress response to surgery.

General Anaesthesia: this is usually the anaesthetic of choice in the paediatric population. Consider premedication on an individual patient basis [3–4].

Regional Anaesthesia: patients with UCDs may have raised intracranial pressure [1–2,4–5,11]. Central neuraxial blockade is contraindicated in patients with signs of raised intracranial pressure. There are no diseas-specific contraindications to peripheral neuraxial blockade. Effective regional anaesthesia provides optimal analgesia and stress response reduction while allowing for a reduction in narcotic administration.

Necessary additional pre-operative testing (beside standard care)

Serum ammonia – a baseline ammonia level is essential to consider the stability of the patient, their suitability for surgery and a potential need for optimisation. Serial measurement may be of benefit in patients at greater risk of acute decompensation, including infants, patients undergoing major surgery, patients with abnormal liver function, symptomatic patients and patients with an unstable disease such as encephalopathy [1–3,5–6]. For ammonia levels of 250-500 μmol^{-1}, haemodialysis (first line) or peritoneal dialysis should be considered, particularly in the presence of symptomatic encephalopathy. Above 500μmol^{-1}, many experts suggest that pre-operative haemodialysis is mandatory [43].

Liver function tests and coagulation studies – patients may have abnormal liver function and coagulation, consider in infants and symptomatic patients (especially in OTCD).

Neuro-imaging studies – consider in patients suspected to have raised intracranial pressure.

Consider the insertion of an arterial of venous blood sampling line in patients requiring multiple peri-operative blood tests. This will minimise psychological and physical stress to patients by reducing the requirement for venepuncture.

Particular preparation for airway management

UCDs are not associated with airway abnormality. Patients who present acutely with decompensation may be actively vomiting [1].

Particular preparation for transfusion or administration of blood products

Patients with UCDs may have abnormal liver function. Coagulopathy is associated with severe elevation of liver enzymes, particularly after the neonatal period [1,10,20]. Transfusion requirements may therefore be increased. Abnormal coagulation has also been observed in asymptomatic patients with OTCD with normal ammonia levels [7].

Hyperammonaemia may also be associated with thrombocytopaenia and platelet dysfunction [21].

Red blood cell transfusions may precipitate hyperammonaemia particularly when stored for long periods, and patients requiring transfusions should be monitored.

Particular preparation for anticoagulation

Patients with UCDs may have abnormal liver function, elevated PT and/or PTT and thrombocytopaenia. Therefore, the use of anti-coagulants should be carefully monitored.

Particular precautions for positioning, transportation and mobilisation

Patients with advanced disease may have contractures and fixed flexion deformities requiring bespoke joint care.

Particular care must be taken during the transportation, positioning and mobilisation of awake patients. Patients may be cognitively impaired with developmental delay, learning and intellectual disabilities [1–2,7,43]. Patients may also have attention deficit hyperactivity disorder or executive function deficits [1–2,22–23].

Interactions of chronic disease and anaesthesia medications

Caution with:

Hypotonic fluids – caution due to a potentially already elevated intracranial pressure. Lowering the sodium concentration may further the increase of an already pre-existing cerebral oedema.

Isotonic fluids – caution due to already high sodium load received from ammonia scavenging medication, e.g. sodium benzoate and phenylacetate/phenylbutyrate. The sodium concentration has to be measured.

Paracetamol – caution due to potential for liver toxicity in patients with abnormal liver function.

Intraoperative agents to avoid:

Systemic corticosteroids – systemic corticosteroids should only be given when urgently indicated (e.g. hydrocortisone for the treatment of anaphylaxis etc.). They should not be given as prophylactic medication (e.g. dexamethasone for post-operative nausea and vomiting). Systemic corticosteroids cause catabolism which can trigger a hyperammonaemic crisis

[1,24]. Case series demonstrate elevated ammonia with perioperative corticosteroid administration [4].

Butyrophenones, e.g. haloperidol, droperidol – may induce hyperammonaemia [25–26].

Sodium valproate – has been associated with hyperammonaemia [27–28].

Anaesthetic procedure

Prior to anaesthesia discuss UCD patients with a metabolic specialist team to define peri-operative medications and an intravenous hydration/fluid regime.

Perioperative management aims to avoid metabolic decompensation by minimising physical and psychological stress; maintaining optimal hydration status; preventing protein catabolism and facilitating nitrogen excretion [1–4,10,18–19].

There are no special considerations regarding the usage of inhalational or intravenous induction agents (ketamine has been uneventfully used in cases of severe UCDs [4]).

The uneventful use of non-depolarising neuromuscular receptor blocking drugs is also described in the literature [3–4], but blockade may theoretically be prolonged in the presence of liver dysfunction.

Optimising hydration:

1. Minimise peri-operative fasting time
    - Timing of procedures requiring perioperative fasting: if feasible, perform UCD patients first on the afternoon list. This allows for an early breakfast and preoperative glucose polymer containing drinks.
    - Children may consume clear fluids up to one hour pre-operatively without increased risk of pulmonary aspiration [29].

2. Start pre-operative maintenance fluids with commencement of peri-operative fast
    - 10mol potassium in 500mol of 10% dextrose or 10% dextrose/0.45% saline (dependant on sodium load from regime of ammonia scavenging medication).

Prevent protein catabolism:

1. Start caloric maintenance fluids with commencement of perioperative fast
    - 10-25% dextrose containing infusion.
    - Intra-lipid solutions may also be required.

2. Minimise perioperative anxiety
    - Consider premedication – patients have safely received midazolam [3–4]. There are no known anaesthetic drug interactions.

3. Ensure patients well analgesed to blunt the stress response
    - Multi-modal analgesia incorporating regional anaesthesia, caution with paracetamol.
    - Analgesia prior to laryngoscopy and start of procedure.

4. Ensure effective antiemesis

- Dexamethasone is contra-indicated [1–2,4,24].
- Caution is advised with droperidol. The use of droperidol has not been described in UCDs. There are case reports of hyperammonaemia induced by the butyrophenone haloperidol [26,30].

Minimise ingestion of additional protein load:

1. Consider nasogastric tube or/and throat pack in procedures where oral or intestinal bleeding is a possibility [31].

- Blood in the stomach constitutes a protein load and can precipitate acute metabolic decompensation.

Facilitate nitrogen excretion:

1. Discuss medication doses with metabolic specialist team. The patient may need:

- Conversion to intravenous ammonia scavenging medication,
- Increased doses especially with major surgery.

2. Common perioperative intravenous drugs:

- Nitogen scavenging medications: these react with glycine and glutamine to form products more readily excreted by the kidneys [32].
  - Ammonul® – a combination of sodium benzoate and sodium phenylacetate,
  - sodium phenylbutyrate,
  - glycerol phenylbutyrate.
- Dietary supplements: required to meet normal physiological needs in UCDs [32]
  - arginine hydrochloride (normally synthesised in the urea cycle); avoid in argininemia,
  - citrulline, carnitine.

3. In rare cases, a peri-operative dialysis may be appropriate (ammonia levels above 500µmol $^{-1}$).

Standard perioperative maintenance regime of ammonia scavenging medication [1–2,32–35,43]:

- *Discuss regimen with metabolic specialist team – individualised patient dosing may vary.*
- *Caution when delivering doses based on weight > 20 kg.*
- *In patients over 20 kg, dosing should be based on body surface area rather than body weight.*

	Minor Surgey	Major Surgey
Sodium benzoate *(to be given iv in 10% dextrose)*	250 mg/kg/day	500 mg/kg/day
Sodium phenylbutyrate or Sodium phenylacetate *(to be given iv in 10% dextrose)*	250 mg/kg/day	500 mg/kg/day
Arginine *(to be given iv in 10% dextrose)*		150-400 mg/kg/day

Infusion Preparation:

- Sodium benzoate and sodium phenylbutyrate can be mixed together in 10% glucose (maximum concentration = 50 mg/ml of each drug).
- Ammonul® is a combination of sodium benzoate and sodium phenylacetate – see product information for guidance on administration.
- Arginine should be diluted separately in 10% glucose (maximum concentration = 50 mg/ml).

Infusions may be piggy-backed into the main 10% dextrose infusion.

Particular or additional monitoring

None required. Consider the insertion of an arterial of venous blood sampling line in patients requiring multiple peri-operative blood tests. In children, consider asleep venous cannulation. The aim is to minimise psychological and physical stress to patients by reducing the frequency of venepuncture. Stress can precipitate a hyperammonaemic crisis and acute decompensation [10] and serial blood gasses and ammonia levels can pick these complications up early.

Possible complications

Acute metabolic decompensation can result in an acute hyperammonaemic crisis. Immediate treatment is required to prevent neurological damage, morbidity and mortality.

In awake patients, this may be characterised by lethargy, irritability, headache, vomiting, altered consciousness, seizure activity and coma. In anaesthetised and paralysed patients, clinical signs are limited, and regular serum ammonia levels are vital.

Immediate treatment requires cessation of protein intake, the promotion of waste nitrogen excretion and reversal of catabolism by optimisation of caloric intake and treatment of the underlying precipitant.

Promote nitrogen excretion:

1. Haemodialysis

2. Ammonia scavenging medications react with glycine and glutamine to form alternative products more readily excreted by the kidneys than ammonia:

- Sodium benzoate is conjugated to glycine to form hippurate which is rapidly excreted in the urine (approximately 1 mol of nitrogen excreted for each mol administered).
- Sodium phenylbutyrate is excreted in the urine as phenylacetylglutamine. It is first oxidised to phenylacetate, then conjugated with glutamine to form phenylacetylglutamine (approximately 2 mol of nitrogen excreted for each mol administered).
- L-arginine is normally synthesised in the urea cycle, so is deficient in OTCD. L-arginine is substraterequired for protein synthesis and ammonia excretion and so requires supplementation to meet normal physiological needs in all UCD's with the exception of argininaemia.
- Citrulline and carnitine

Emergency dosing regimen [32–36,43]:

- Treatment aims to restore normal ammonia levels.
- Discuss regimen with metabolic specialist team, dosing may vary dependent on patient.
- In patients over 20 kg, dosing should be based on body surface area rather than body weight.

	Loading Dose *(given over 90-120 minutes)*	Maintenance Dose
Sodium benzoate *(to be given iv in 10% dextrose)*	250 mg/kg	250 mg/kg/day
Sodium phenylbutyrate or Sodium phenylacetate *(to be given iv in 10% dextrose)*	250 mg/kg	250 mg/kg/day
Arginine *(to be given iv in 10% dextrose)*	250-400 mg/kg (1-2 mmol/kg) (Not always given)	250 mg/kg/day (1.2mmol/kg/day)
N-carbamylglutamate **(***only available as oral/ enteral drug preparation)**	100 mg/kg bolus per NG tube	25-62.5 mg/kg every 6 h

Infusion Preparation:

- Sodium benzoate and sodium phenylbutyrate can be mixed together in 10% glucose (maximum concentration = 50 mg/ml of each drug).
- Ammonul® is a combination of sodium benzoate and sodium phenylacetate – see product information for guidance on administration.
- Arginine should be diluted separately in 10% glucose (maximum concentration = 50 mg/ml).

Reverse Catabolism:

1. Optimise analgesia and depth of anaesthesia.
2. Increase caloric intake:
   - 10-25% intravenous dextrose providing 8–10 mg/kg^{-1} min^{-1} of glucose.
   - Intralipid solutions.

Treat underlying precipitant:

Common precipitants include sepsis (particularly neonates, infants and children), prolonged fasting, the puerperium, drugs (corticosteroids, butyrophenones), crush injuries, perioperative chemotherapy/radiotherapy and perioperative high protein diets [3–4,7,10,24–26,36,43].

Post-operative care

Effective pain control and anti-emesis is required to minimise physical and psychological stress. This will reduce the risk of acute decompensation and hyperammonaemia by minimising protein catabolism.

Consider intensive and high dependency care on an individualised patient basis.

Maintain optimal hydration status by resuming the patients' normal/specialist UCD diet at the earliest opportunity. Classically, this is a high caloric, low protein regime supplementing arginine, citrulline and oral alternative pathway therapy [3–4]. Only discontinue intravenous therapy when normal diet resumed.

Disease-related acute problems and effect on anaesthesia and recovery

Perioperative physiological/psychological stressors such as prolonged fasting, dehydration, the surgical stress response, perioperative anxiety, or suboptimal analgesic management result in increased protein catabolism. Protein breakdown results in accumulation of glutamate and ammonia, metabolic decompensation and a potentially fatal hyperammonaemia [2–4].

Ambulatory anaesthesia

Consult the metabolic specialist team regarding the appropriateness of same day discharge. This must be decided on an individual patient basis taking into consideration the type of procedure and the stability of the patient.

Obstetrical anaesthesia

Patients are at risk of becoming catabolic and suffering acute metabolic decompensation and hyperammonaemia during pregnancy, especially post-partum [1–2,24,37–40]. There is some suggestion of placental transfer of ammonia from the maternal compartment to the foetus, however, the clinical significance of this remains unquantified [41].

A multi-disciplinary metabolic, anaesthetic and obstetric plan is required ante-natally to minimise physical and psychological stress; maintain optimal hydration status; prevent protein catabolism and facilitate nitrogen excretion.

Ante-natal metabolic plan

- This requires adaptation of a patient's pre-pregnancy drug protocol, early cannulation and administration of maintenance 10% dextrose with appropriate electrolytes and the addition of intralipids as needed to meet caloric requirements.
- Breastfeeding mothers are at risk of becoming catabolic and suffering acute metabolic decompensation and hyperammonaemia post-delivery. Therefore, it is important that the multidisciplinary metabolic and obstetric plans take this into account.

Central neuraxial blockade is beneficial

- Caution: patients with UCD may have raised intracranial pressure, this must be excluded [1–2,4–5,11].
- Consider early epidural in the first stage of labour to blunt the stress response.
- Caesarean section may be performed uneventfully under epidural, spinal or general anaesthesia [42].

Avoid hypovolaemia and dehydration.

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