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Urea cycle disorders

Waardenburg syndromes

orphanaesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 14 | 2021

OrphanAnesthesia –

ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

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OrphanAnesthesia –

a project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

Find a survey of the recommendations published until now on:

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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, Carbamoyl phosphate synthetase 1 deficiency, CPS1D	ICD 10: E72.2
Disease name:	**Ornithine transcarbamylase deficiency** Synonyms: OTC deficiency, OTCD	ICD 10: E72.4
Disease name:	**Ornithine transcarbamylase deficiency** Synonyms: Argininosuccinate 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 deficiency (ASSD/citrullinaemia type 1), argininosuccinate lyase deficiency (ASLD), arginase-1 deficiency and N-acetylglutamate synthase deficiency (NAGSD).

The peri-operative 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

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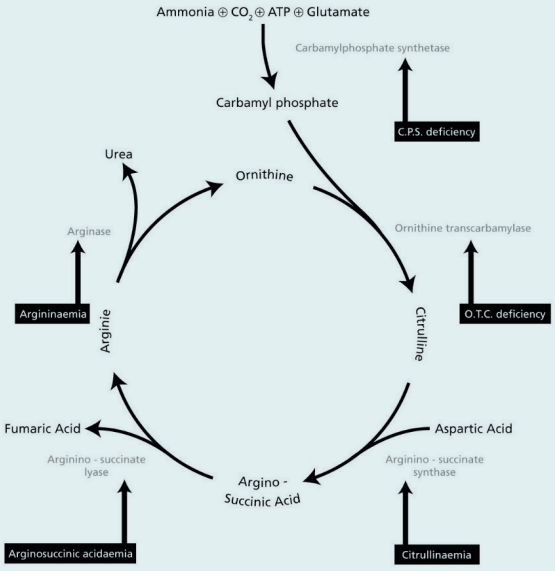
exceed current estimation due to the absence of reliable new-born screening and under-diagnosis of fatal cases. Multiple mutations have been recognised and some disorders such as OTCD have heterogeneous penetrance and phenotypes, due to variability in gene activation and hepatocyte expression [1,2,8–15,43].

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 carbamoylphosphate to urea and results in the accumulation of ammonia and, depending on the disorder in question, also citrulline (argininosuccinate synthetase deficiency), argininosuccinic acid (argininosuccinate lyase deficiency), fumaric acid (arginase-1 deficiency), glutamine (carbamoyl phosphate 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/citrullinaemia 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

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(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. Peri-operative 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

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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 hyperammonaemic 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 disease-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 venipuncture.

Particular preparation for airway management

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

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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

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[1,24]. Case series demonstrate elevated ammonia with peri-operative 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.

Peri-operative 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 peri-operative fasting: if feasible, perform UCD patients first on the afternoon list. This allows for an early breakfast and pre-operative 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
    - 10 mol potassium in 500 mol of 10 % dextrose or 10 % dextrose/0.45 % saline (dependent on sodium load from regime of ammonia scavenging medication).

Prevent protein catabolism:

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

2. Minimise peri-operative 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.

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4. Ensure effective anti-emesis

- 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 peri-operative intravenous drugs:
   - Nitrogen 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 cases of argininaemia,
     - citrulline, carnitine.

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

Standard peri-operative 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 surgery	Major surgery
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 venipuncture. 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, thus it is deficient in OTCD. L-arginine is a substrate required for protein synthesis and ammonia excretion and thus requires supplementation to meet normal physiological needs in all UCDs with the exception of argininaemia.
- Citrulline and carnitine.

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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 (1.2 mmol/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, peri-operative chemotherapy/radiotherapy and peri-operative 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 mini-mising 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

Peri-operative physiological/psychological stressors such as prolonged fasting, dehydration, the surgical stress response, peri-operative 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 antenatally 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 anaesthesia 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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References

1. Tuchman M, Lee B, Lichter-Konecki U, Summar ML, Yudkoff M, Cederbaum SD, et al. Cross-sectional multicenter study of patients with urea cycle disorders in the United States. Mol Genet Metab 2008;94:397–402
2. Brusilow SW, Horwich AL. Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds.). The Metabolic and Molecular Bases of Inherited Disease, 8th ed., New York: McGraw-Hill, 2001:1909–1963
3. Dutoit AP, Flick RR, Sprung J, Babovic-Vuksanovic D, Weingarten TN. Anesthetic implications of ornithine transcarbamylase deficiency. Pediatr Anesth 2010;20:666–673
4. Schmidt J, Kroeber S, Irouschek A, Birkholz T, Schroth M, Albrecht S. Anesthetic management of patients with ornithine transcarbamylase deficiency. Pediatr Anesth 2006;16: 333–337
5. Maestri NE, Clissold D, Brusilow SW. Neonatal onset ornithine transcarbamylase deficiency: a retrospective analysis. J Pediatr 1999;134:268–272
6. Wraith JE. Ornithine carbamoyltransferase deficiency. Arch dis child 2001;84.1:84–88
7. Lichter-Konecki U, Caldovic L, Morizono H, Simpson K. Ornithine Transcarbamylase Deficiency (1993–2013), in: Pagon RA, Adam MP, Ardinger HH, et al. (eds.) GeneReviews®
8. Arn PH. Hyperammonemia in women with mutation at the ornithine carbamoyltransferase locus. A case of postpartum coma. N Engl J Med 1990;322:1652–1655
9. Honeycutt D, Callahan K, Rutledge L, et al. Heterozygote ornithine transcarbamylase deficiency presenting as symptomatic hyperammonemia during initiation of valproate therapy. Neurology 1992;42:666–668
10. Berry GT, Steiner RD. Long-term management of patients with urea cycle disorders. J Pediatr 2001;138:S56–S60; discussion S60–S61
11. Perpoint T, Argaud L, Blanc Q et al. Fatal hyperammonemic coma caused by ornithine transcarbamylase deficiency in a woman. Intensive Care Med 2001;27:1962
12. Trivedi M, Zafar S, Spalding MJ, Jonnalagadda S. Ornithine transcarbamylase deficiency unmasked because of gastrointestinal bleeding. J Clin Gastroenterol 2001;32:340–343
13. Legras A, Labarthe F, Maillot F, et al. Late diagnosis of ornithine transcarbamylase defect in three related female patients: polymorphic presentations. Crit Care Med 2002;30:241– 244
14. Goddon N. Ornithine transcarbamylase deficiency: a urea cycle defect. Eur J Paediatr Neurol 2003;7:115–121
15. Cavicchi C, Malvagia S, la Marca G, et al. Hypocitrullinemia in expanded newborn screening by LC-MS⁄MS is not a reliable marker for ornithine transcarbamylase deficiency. J Pharm Biomed Anal 2009;49:1292–1295
16. Michalak A, Butterworth RF. Ornithine transcarbamylase deficiency: pathogenesis of the cerebral disorder and new prospects for therapy. Metab Brain Dis 1997;12:171–182
17. Kasahara M, Kiuchi T, Uryuhara K, et al. Treatment of ornithine transcarbamylase deficiency in girls by auxiliary liver transplantation: conceptual changes in a living-donor program. J Pediatr Surg 1998;33:1753–1756
18. Ensenauer R, Tuchman M, El-Youssef M et al. Management and outcome of neonatal-onset ornithine transcarbamylase deficiency following liver transplantation at 60 days of life. Mol Genet Metab 2005;84:363–366
19. Hasegawa T, Tzakis AG, Todo S, et al. Orthotopic liver transplantation for ornithine transcarbamylase deficiency with hyperammonemic encephalopathy. J Pediatr Surg 1995; 30:863–865
20. Mustafa A, Clarke JT. Ornithine transcarbamoylase deficiency presenting with acute liver failure. J Inherit Metab Dis 2006;29:586
21. Shinya H, Matsuo N, Takeyama N, Tanaka T. Hyperammonemia inhibits platelet aggregation in rats. Thrombosis research 1996;81:195–201
22. Gyato K, Wray J, Huang ZJ, Yudkoff M, Batshaw ML. Metabolic and neuropsychological phenotype in women heterozygous for ornithine transcarbamylase deficiency. Ann Neurol 2004;55:80–86
23. Krivitzky L, Babikian T, Lee HS, Thomas NH, Burk-Paull K.,Batshaw ML. Intellectual, adaptive, and behavioral functioning in children with urea cycle disorders. Pediatric research 2009;66:96
24. Lipskind S, Loanzon S, Simi E, Ouyang DW. Hyperammonemic coma in an ornithine transcarbamylase mutation carrier following antepartum corticosteroids. J Perinatol 2011;31:682–684

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25. Rowe PC, Newman SL, Brusilow SW. Natural history of symptomatic partial ornithine transcarbamylase deficiency. New Eng J Med 1986;314:541–547
26. Rubenstein JLR, Johnston K, Elliott GR, Brusilow SW. Haloperidol-induced hyperammonaemia in a child with citrullinaemia. J Inherit Metab 1990;13:754–755
27. Oechsner M, Steen C, Stürenburg HJ, Kohlschütter A. Hyperammonaemic encephalopathy after initiation of valproate therapy in unrecognised ornithine transcarbamylase deficiency. J Neurol Neurosurg Psychiatry 1998;64:680–682
28. Thakur V, Rupar A, Ramsay DA, Singh R, Fraser DD. Fatal cerebral edema from late-onset ornithine transcarbamylase deficiency in a juvenile male patient receiving valproic acid. Pediatr Crit Care Med 2006;7:273–276
29. Thomas M, Morrison C, Newton R, Schindler E. Consensus statement on clear fluids fasting for elective pediatric general anesthesia. Paediatr Anaesth 2018;28:411–414
30. Leao M. Valproate as a cause of hyperammonemia in heterozygotes with ornithine-transcarbamylase deficiency. Neurology 1995;45:593–594
31. Kim TW, Hall SR. Liver transplantation for propionic acidaemia in a 14-month-old male. Pediatr Anesth 2003;13:554–556
32. British Inherited Metabolic Disease Group. Medicines used for the treatment of hyperammonaemia. Available at: http://www.bimdg.org.uk/store/guidelines/UCD-medicines2-330009-22-05-2013.pdf. Accessed on: 07.11.2018
33. British Inherited Metabolic Disease Group. Management of Surgery in Children with Urea Cycle Disorders. Available at: http://www.bimdg.org.uk/store/guidelines/Management_of_surgery_in_children_with_urea_cycle_disorders__215051_09092016.pdf. Accessed on: 07.11.2018
34. British Inherited Metabolic Disease Group. Adult emergency management urea cycle defects. Available at: http://www.bimdg.org.uk/store/guidelines/ADULT_UCD-rev_2015_422170_09012016.pdf. Accessed on: 07.11.2018
35. British Inherited Metabolic Disease Group. Intravenous drug calculators for the emergency treatment of hyperammonemia. Available at: http://www.bimdg.org.uk/store/guidelines/Drug_Calculator_Index_743383_12042017.pdf. Accessed on: 07.11.2018
36. New England Consortium of Medical Programmes. Ornithine Transcarbamylase Deficiency. Available at: newenglandconsortium.org/for-professionals/acute-illness-protocols/urea-cycle-disorders/ornithine-transcarbamylasedeficiency-Otc. Accessed on: 07.10.2018
37. Redonnet-Vernhet I, Rouanet F, Pedespan JM, Hocke C, Parrot F. A successful pregnancy in a heterozygote for OTC deficiency treated with sodium phenylbutyrate. Neurology 2000;54:1008
38. Mendez-Figueroa H, Lamance K, Sutton VR, Aagaard-Tillery K, Van den Veyver I. Management of ornithine transcarbamylase deficiency in pregnancy. Am J Perinatol 2010; 27:775–84
39. Celik O, Buyuktas D, Aydin A, Acbay O. Ornithine transcarbamylase deficiency diagnosed in pregnancy. Gynecol Endocrinol 2011;27:1052–1054
40. Ituk U, Constantinescu OC, Allen TK, Small MJ, Habib AS. Peripartum management of two parturients with ornithine transcarbamylase deficiency. Int J Obstet Anesth 2012;21:90–93
41. Hussamy DJ, Nelson DB, Shivvers SA. Hyperammonemia: A Report of Maternal Biliary Cirrhosis and Neonatal Outcome. Case reports in critical care 2013
42. Lewis M, Singh I, Prasad C, Rupar T, Jones P. Anesthetic management of a parturient with ornithine transcarbamylase deficiency. Can J Anaesth 2007;54:44612–44612
43. Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metabol Dis 2019;42:1192–1230
44. Summar ML, Koelker S, Freedenberg D, et al. The incidence of urea cycle disorders. Mol Genet Metab 2013;110:179–180.

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