

# A&I

## ANÄSTHESIOLOGIE & INTENSIVMEDIZIN

Offizielles Organ: Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e. V. (DGAI)  
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Organ: Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin e. V. (DIVI)



**Argininosuccinate Lyase Deficiency**

orphan**anesthesia**

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

### SUPPLEMENT NR. 6 | 2024

## 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 Patientinnen und Patienten mit seltenen Erkrankungen. Damit will OrphanAnesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patientinnen und 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 Anästhesistinnen und Anästhesisten damit keine Erfahrungen gesammelt haben, sodass 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 eine Anästhesistin bzw. ein Anästhesist sowie eine weitere Krankheitsexpertin bzw. ein weiterer Krankheitsexperte (z. B. Pädiaterin bzw. Pädiater oder Neurologin bzw. Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, sodass 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](http://www.ai-online.info) veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

## 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 recommendations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via [www.ai-online.info](http://www.ai-online.info). As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

**Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:**

[www.ai-online.info/Orphsuppl](http://www.ai-online.info/Orphsuppl)  
[www.orphananesthesia.eu](http://www.orphananesthesia.eu)

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# orphananesthesia

Anaesthesia recommendations for patients suffering from

## Argininosuccinate Lyase Deficiency

**Disease name:** Argininosuccinate lyase deficiency

**ICD 10:** E72.2

**Synonyms:** ASA deficiency, ASL deficiency, argininosuccinase deficiency, argininosuccinate lyase deficiency, argininosuccinic acid lyase deficiency

**Disease summary:**

Argininosuccinate lyase (ASL) deficiency, also known as argininosuccinic aciduria (AA), is the result of a mutated or deficient argininosuccinate lyase enzyme. This defective or deficient enzyme leads to inadequate ureagenesis, accumulation of argininosuccinic acid, and deficient endogenous arginine production. Aside from the hyperammonaemia pervasive to urea cycle disorders as a group, ASL deficiency is specifically associated with higher rates of neurocognitive deficits, liver disease, trichorrhexis nodosa (coarse brittle hair), impairment of creatinine clearance, chronic diarrhoea, and systemic hypertension. Electrolyte imbalances of unclear etiology have been identified, even in patients not treated with nitrogen scavenging drugs. This may be due to increased renal wasting. Nitrogen scavenging therapy (such as sodium benzoate or sodium phenylbutyrate) may lead to hypernatraemia and hypokalaemia. Like other urea cycle disorders, this disease is rare, with an incidence of approximately 1/70,000. ASL deficiency is passed via autosomal recessive inheritance and may manifest in one of two forms: neonatal onset disease or a less severe late-onset form.

Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong



Find more information on the disease, its centres of reference and patient organisations on Orphanet: [www.orpha.net](http://www.orpha.net)

► **Citation:** Sisk JM, Scales L, Polan MB: Argininosuccinate Lyase Deficiency. Anästh Intensivmed 2024;65:S124–S132. DOI: 10.19224/ai2024.S124

### Disease summary

#### **Pathophysiology:**

The urea cycle is a hepatic pathway which converts excess nitrogen to urea. Urea is then excreted via renal pathways. As the breakdown of protein results in an increased nitrogen burden, urea cycle metabolism increases during physiologic states predominated by catabolism. Stressors such as sepsis, surgery, fasting, consumption of high-protein meals or heavy exercise may all induce catabolic metabolism.

If the urea cycle is impaired, nitrogen accumulates in the form of ammonia. Hyperammonaemia may be harmful to multiple organ systems. This may be particularly damaging to the neurocognitive system. Significant hyperammonaemia may lead to encephalopathy associated with vomiting, lethargy, seizure, central respiratory depression and death.

Aside from the hyperammonaemia that results from inadequate ureagenesis, patients with ASL deficiency experience symptoms related to decreased endogenous arginine and increased argininosuccinic acid. Human hair consists of more than 10% arginine by weight. Without supplementation, patients exhibit weak brittle hair often surrounded by alopecia to some degree. Arginine deficiency may also cause systemic hypertension due to a secondarily reduced synthesis of nitric oxide. Conversely, excess argininosuccinic acid may be culpable for the liver disease observed in some ASL-deficient patients. Additionally, specific neurocognitive deficits (including increased incidence of ADHD and seizure activity) are associated with the disorder, the pathophysiology of which remains unclear at this time.

#### **Presentation:**

Neonatal onset of the disease is clinically more severe and is of acute concern similar to other urea cycle disorders with hyperammonaemia. Neonates are often asymptomatic for the first 24–48 hours, before exhibiting lethargy, vomiting and feeding difficulties. Neonates initially present with tachycardia and tachypnea, which progresses to respiratory depression, seizures and death as ammonia accumulates. In the early stages of disease, ASL deficiency may be difficult to distinguish from other commonly presenting urea cycle disorders. However, specific to ASL deficiency, cases of neonatal onset may exhibit the hallmark manifestations of liver disease or trichorrhexis nodosa. Alternatively, the late-onset disease is characterised by transient hyperammonaemia. Triggers may include stress, infection, dietary changes or any other event resulting in a predominately catabolic state.

#### **Management:**

Long-term management focuses on the prevention of metabolic crises by way of significant lifestyle modification, concomitantly supplementing patients with exogenous arginine. These lifestyle modifications include strict adherence to a stable diet that restricts protein and avoids fasting in an attempt to maintain anabolism. Metabolic decompensations resulting in hyperammonaemia require immediate medical attention. If ammonia levels do not normalise with medical management, haemodialysis may be required. Orthotopic liver transplantation may be considered in patients with recurrent decompensation resistant to medical therapy.

#### **Prognosis:**

Due to the rarity of the disease and its variable presentation, a prognosis is difficult to assess. In general, life expectancy will be decreased, with over 65% of long-term survival (Baruteau et al 2017) and 80% of the patients expiring before the age of 20, regardless of their age at the onset of disease. The implementation of new treatment strategies has resulted in greater survivability of infants with neonatal onset disease. However, this increase in survival is accompanied by a significant increase in intellectual disability.

### Centres

Surgery should only be carried out in centres prepared for dealing with acute hyperammonemic decompensations and should not be performed in the outpatient setting.

### Typical surgery

- ENT procedures (bilateral myringotomy tubes, tonsillectomy and adenoidectomy) may be performed to decrease the risk of recurrent infections leading to metabolic crisis.
- General surgery procedures such as gastrostomy tube placement, anti-reflux procedures such as Nissen fundoplication and vascular access procedures are all common.
- Dental procedures under anaesthesia may be required due to developmental delay
- Anaesthesia may be necessary for diagnostic procedures such as CT or MRI.
- Emergency procedures such as appendectomy or trauma surgery
- Some children may require liver transplant for recurrent hyperammonaemia and/or liver failure.

### Type of anaesthesia

- There are insufficient data to support the superiority of any particular anaesthetic agent or technique.
- Induction:
  - Sevoflurane, sodium thiopental, isoflurane, propofol and nitrous oxide have all been reported to be safe for induction of anaesthesia in other urea cycle disorders.
- Maintenance:
  - Sevoflurane, isoflurane, nitrous oxide have been safely used for the maintenance of anaesthesia in other urea cycle disorders.
  - Midazolam, s-ketamine, fentanyl and morphine in combination with surgical infiltration of ropivacaine have been reported as safe anaesthetic agents in other urea cycle disorders.
  - Pancuronium, atracurium, cisatracurium and vecuronium have been used without prolongation of neuromuscular blockade in other urea cycle disorders.
- Drugs that induce catabolism such as dexamethasone or other steroids should be avoided.
- Any anaesthetic agent should be used with caution and vigilant postoperative monitoring as the stress of surgery alone may trigger a metabolic crisis.
- ENT or dental procedures with potential bleeding into the GI tract should utilise OG tubes and/or throat packs to minimise the amount of blood ingested as this protein load may represent a metabolic stressor leading to decompensation.
- General anaesthesia should be used with caution and appropriate postoperative monitoring in conjunction with a clinical geneticist or metabolic physician.

### **Necessary additional diagnostic procedures (preoperative)**

- The following laboratory values should be evaluated preoperatively:
  - Blood glucose
  - Serum electrolytes
    - Patients may experience hypernatraemia and hypokalaemia
      - More common in patients receiving sodium phenylbutyrate or sodium benzoate therapy
  - Plasma ammonia
    - Serves as a direct indicator of toxicity
  - Liver function tests
  - Coagulation studies
    - Patients with ASL deficiency are predisposed to hepatic dysfunction with resultant disruption of coagulation pathways
  - Arterial or venous blood gas may be considered.

### **Particular preparation for airway management**

There are no specific recommendations or disease related concerns regarding airway management.

### **Particular preparation for transfusion or administration of blood products**

There are no specific recommendations for the transfusion of blood products.

### **Particular preparation for anticoagulation**

Patients with argininosuccinate lyase deficiency do not routinely require anticoagulation.

### **Particular precautions for positioning, transport or mobilisation**

There are no specific recommendations or disease-related concerns regarding the positioning of these patients.

### **Probable interaction between anaesthetic agents and patients' long-term medication**

Specific interactions between maintenance medications and routine anaesthetic medications do not exist. Iatrogenic hypernatraemia should be avoided as sodium containing IV fluids and sodium benzoate in addition to maintenance sodium phenylbutyrate represent a significant sodium burden. 1g sodium benzoate contains 7mmol sodium and 1g phenylbutyrate contains 5.4mmol sodium. Long-term medications should be maintained before and after surgery with conversion to IV formulations if necessary.

### Anaesthetic procedure

- Involve a clinical geneticist or metabolic physician in advance for preoperative planning
  - Patients routinely take sodium phenylbutyrate or glycerol phenylbutyrate or/and sodium benzoate (ammonia scavengers) and arginine (substrate for urea cycle metabolism beyond the deficient enzyme)
    - Glycerol phenylbutyrate is a clear liquid medication and may be taken preoperatively prior to elective surgery.
    - Ammonia scavenging medication should not be taken or given prior to elective surgery
- Elective surgery should not be performed in the outpatient setting
  - Patients should not fast for prolonged periods
    - Patients should be first on the surgical schedule
- Labs:
  - Blood glucose
  - Serum electrolytes
  - Plasma ammonia
    - Serves as a direct indicator of toxicity
  - Liver function tests
  - Coagulation studies
    - Patients with ASL deficiency are predisposed to hepatic dysfunction with resultant disruption of coagulation pathways.
- Identify catabolic stressors (e.g., infection, trauma, etc.)
  - Treat aggressively
- Avoid intraoperative hypothermia
- Minimise protein intake
- Optimise hydration
  - The night before surgery: 10% glucose solution with electrolytes should be infused at a rate to ensure anabolic metabolism
  - This solution should be continued until the patient is known to be tolerating enteral nutrition
- Minimise catabolic metabolism
  - The patient should preferably be kept in a state of anabolic metabolism
- Promote nitrogen excretion
- It has been suggested to avoid prophylactic antiemetic therapy as nausea and vomiting are early signs of metabolic decompensation [9]
- Rapid extubation is recommended in order to facilitate an evaluation of consciousness, nausea and vomiting as signs of metabolic decompensation.

### Particular or additional monitoring

Electrolytes, ammonia levels and blood glucose should be evaluated preoperatively. For prolonged procedures, intraoperative monitoring of arterial or venous blood gas, glucose and ammonia levels should be considered.

### Possible complications

Patients are prone to life-threatening hyperammonaemia which may progress to coma, brain damage and death within hours.

### Postoperative care

- Patients should be observed postoperatively for signs of hyperammonaemia in coordination with a clinical geneticist or metabolic physician.
- Arterial or venous blood gas, electrolytes and serum ammonia should be evaluated postoperatively every 6 hours during the first 24 hours
  - These labs should also be checked if the patient experiences signs of metabolic decompensation such as vomiting, lethargy, tachypnoea or seizures.
- Glucose-containing IV fluids should be continued until the patient tolerates enteral nutrition.
- Oral feeds should be resumed as soon as possible to ensure optimal caloric intake and anabolic metabolism.
- In the first 24 hours after surgery, it is recommended to follow the emergency regimen applying to periods of metabolic stress (such as surgery, infection, vomiting or diarrhoea).
- In the following days, proteins can be introduced progressively
  - IV administration of glucose should stop only when the patient is well and metabolically stable.
- In case there is intolerance of feeding, lipids must be added to the IV solution.
- Ambulatory surgery is not recommended.

### Information about emergency-like situations / Differential diagnostics

- Patients are prone to life-threatening hyperammonaemia which may progress to coma, brain damage and death within hours
  - This may be triggered by:
    - Fasting
    - Poor feeding
    - Surgical stress
    - Hypothermia
    - Minor infections
    - Mild dehydration
    - Vomiting/diarrhoea
    - Medication noncompliance
    - Corticosteroids
    - Dietary noncompliance
      - High protein intake
      - Failure to take metabolic formula mix or low-energy intake
  - Signs of metabolic crisis include:
    - Anorexia
    - Nausea/vomiting
    - Lethargy
    - Abnormal respiratory pattern
    - Spasticity
    - Hyperreflexia/clonus
- A clinical geneticist or metabolic physician should be contacted immediately if signs of metabolic crisis are present
  - Recommended work-up:
    - Evaluate and treat any triggers

- Check STAT ammonia level
- Check CBC, CMP, ABG
- Emergency treatment:
  - Cease all protein intake
    - Patient should be made NPO
  - Generous IV hydration to correct dehydration
    - IV Normal saline boluses
      - Avoid lactated Ringers
    - Maintenance IVF with fluids containing D10% (or greater) at 1.5x maintenance rate
  - Start IV intralipid therapy
  - IV ammonia scavenger (Ammonul) therapy and IV arginine
  - Acidosis may be corrected slowly with sodium bicarbonate
  - Critically high ammonia levels ( $>400\mu\text{mol/L}$  in children and  $>200\mu\text{mol/L}$  in adults) may require emergent dialysis

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#### Ambulatory anaesthesia

Ambulatory surgery should not be performed in patients with argininosuccinate lyase deficiency due to the possibility of surgical stress triggering a metabolic crisis which may not present until the postoperative period.

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#### Obstetrical anaesthesia

Successful pregnancy has been described in patients suffering from argininosuccinate lyase deficiency [13]. There is no evidence to support the superiority of regional or general anaesthesia in these patients. The choice of anaesthetic technique should be dictated by the clinical situation. Clinical geneticists or metabolic physicians should be involved early in the prenatal care of these patients. Patients should be monitored for signs of metabolic crisis throughout labour, delivery and the postpartum period. Involution of the postpartum uterus may trigger protein catabolism and metabolic decompensation. Anabolic metabolism should be ensured during delivery and the postpartum period. Glucose-containing IV solutions should be maintained until tolerance of feeding has been documented.

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dürften.

## Wichtiger Hinweis

Für Angaben über Dosierungsanweisun-  
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Verlag und den Herausgebern keine Ge-  
währ übernommen werden. Derartige An-  
gaben müssen vom jeweiligen Anwender  
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Gleiches gilt für berufs- und verbands-  
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I would like to participate in the project

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