orphanesthesia

Anesthesia recommendations for

Porphyrias

Disease name: Porphyria

ICD 10: E80.0, E80.1, E80.2

ORPHAcode: 738, 95157, 309813, 659681, 659694, 659698

Synonyms: ALA dehydratase deficiency porphyria (ADP), Acute intermittent porphyria (AIP), Congenital erythropoietic porphyria (CEP), Erythropoietic protoporphyria (EPP), Hereditary coproporphyria (HCP) Porphyria cutanea tarda (PCT), Variegate porphyria (VP), X-linked protoporphyria (XLEPP)

Brief disease summary: Porphyrias are a group of metabolic disorders, mainly inherited, in which there are defects in the heme biosynthetic pathway that may lead secondarily to overproduction or accumulation of one or more heme precursors. Heme is essential for biotransformation (respiratory chain, cytochromes P-450, and other heme-containing enzymes) and transport of oxygen from the lungs to tissues. Mainly, eight different enzymes are involved in the biosynthesis of heme. In acute porphyrias, the activity of the entire pathway is chiefly related to induction and end-product repression of activity of the first and normally rate-controlling enzyme in liver cells, namely 5-aminolevulinic acid (ALA) synthase 1 (ALAS1). Hepatic heme deficiency leads to up-regulation of ALAS1 by several molecular mechanisms, whereas sufficiency or excess of heme leads to down-regulation of ALAS1 through a multitude of effects on gene transcription and translation. In contrast in erythropoiesis another variant, namely ALAS2 regulates heme biosynthesis by iron and erythropoietin [1,2].

Diagnosis may be incorrect; if uncertainty exists, the diagnosis should be re-evaluated.

Every patient is unique; individual circumstances must always guide clinical care.

Medicine is in progress; new clinical knowledge may not be yet reflected in this recommendation.

Recommendations are not rules or laws; they provide a framework to support clinical decision-making. Although this recommendation has passed a structured review process, it does not meet the formal criteria of a guideline.

Translations may not always reflect the most recent updates of the English version.

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

Emergency information

A	**AIRWAY / ANESTHETIC TECHNIQUE**	No typical airway difficulties expected.
B	**BLOOD PRODUCTS (COAGULATION)**	None.
C	**CIRCULATION**	Acute attacks may be associated with hypertension, tachycardia and electrolyte abnormalities.
D	**DRUGS**	As drugs can trigger acute porphyria attacks, check for contraindications, e.g. using appendix 1. In a life-threatening emergency situation, any necessary medication can be administered, even if that medication is or could be a porphyrinogen, since any induction of hepatic heme synthesis can be neutralized with heme (e.g., Normosang® or Panhematin®).
E	**EQUIPMENT**	Operation room: yellow light filters protect organ damage in porphyrias with light sensitivity (PCT, EPP, XLEPP, CEP, VP, HCP).

Additional disease information

With except of sporadic PCT, the enzyme deficiency disorders follow either an autosomal dominant, autosomal recessive or X-linked inheritance. There are at least eight different forms of porphyrias. Depending on the chief site of overproduction of heme precursors, porphyrias are classically divided into hepatic or erythropoietic types. Another useful classification is according to cardinal clinical manifestations: Four of the diseases may give rise to acute attacks with neuro-visceral manifestations [the acute or inducible porphyrias AIP, VP, HCP, ADP] and these are a major issue concerning anesthesia. Other forms cause cutaneous manifestations. However, for two of the acute porphyrias, namely, hereditary coproporphyria (HCP) and variegate porphyria (VP), patients may have both neuro-visceral and cutaneous manifestations. The non-acute cutaneous porphyrias do not exhibit the acute symptoms of neurological disorders, abdominal pain and electrolyte abnormalities and in particular they are not triggered by anesthetic agents or any drugs. Therefore, they do not present a serious peri-operative risk [3].

However, patients with cutaneous blistering type (PCT, VP, HCP, CEP) and non-blistering type (EPP, XLEPP) present with light sensitivity on exposed skin areas. Artificial light, incandescent light, in particular used for operation procedures, can cause blindness and extremely severe

skin and visceral reactions. Special yellow light filters are needed to absorb visible light within the Soret band (nearly 400 nm). UV protection is not sufficient [3].

Acute porphyria attacks hardly ever occur before puberty. In a Delphi process, a porphyria attack was defined as an episode that typically lasts more than 24 hours, with a significantly, more than 10-fold upper the normal cut off, increased urinary porphobilinogen/creatinine ratio and at least two of the following symptoms:

- Intense pain, most common in the abdomen
- Nausea, vomiting, and/or tachycardia
- Hyponatremia
- Peripheral neurpoathy
- Urinary retention or incontinence
- Central nervous system involvement (e.g., seizures, confusion, psychosis).

Attacks can worsen rapidly and also lead to arrhythmias [4].

Acute porphyrias are mainly diseases of women in their child-bearing years [Ages 18-50 years]. Incidence and prevalence vary depending on the underlying genetic defect and show regional differences. In most countries, AIP is the most common and most severe form of acute porphyria, with symptomatic disease occurring in about 1:100 000. In patients with psychiatric disorders, the prevalence may be higher, perhaps as high as 210: 100000. The prevalence of genetic defects in the hydroxymethyl bilane synthase (HMBS) gene [also known as porphobilinogen deaminase] is far higher, about 1/1600 individuals in Western Europe, emphasizing the importance of other genetic or acquired factors in pathogenesis. Both, symptomatic and asymptomatic heterozygotes, display about 50 percent of porphobilinogen deaminase activity in the majority of individuals; a total deficiency is not reconcilable with life. 99 percent of individuals with the enzyme deficiency exhibit never clinical signs. In affected families the penetrance is higher (about 23%). Trigger factors induce ALA-synthetase 1 in liver and may exacerbate the disorder. Important factors for hepatic overproduction are infections (such as Covid19), starvation, alcohol, smoking, stress, induction of hepatic CYP 450 by xenobiotics and drugs (such as barbiturates) pregnancy and female hormones (progesterone) [3,5-8].

Other Symptoms: Acute attacks occur after puberty, commonly in females, cause abdominal pain, obstipation, nausea, autonomic instability (hypertension, tachycardia, neuropathy, motility disorder), muscle weakness, paresthesia, neuropsychiatric abnormalities (depression, hallucinations, “brain fog”), electrolyte abnormalities (hyponatremia, hyopomagnesemia) [8,9].

Notably, a novel agent (Givosiran, Alnylam Pharmaceuticals, Cambridge, MA) that addresses the underlying pathology of AIP promises high efficacy with a tolerable side effect profile. Givosiran is a small interfering RNA that neutralizes excess ALAS1 mRNA in hepatocytes. The small interfering RNA is conjugated to trimeric N-acetyl-galactosamine. After subcutaneous injection, Givosiran is directed to and endocytosed by hepatocytes that carry the N-acetylgalactosamine binding asialoglycoprotein receptor. Once endocytosed, the small interfering RNA is cleaved from the conjugate to potently reduce levels of ALAS1 mRNA and protein. A phase 3 trial (Envision) showing a significant reduction in the annualized rate of porphyria attacks, days of administered heme, and urinary ALA levels with Givosiran. Moreover, Givosiran has been used successfully for treatment of chronic symptoms in patients with AIP [5, 7].

Typical surgery and procedures

None.

Because patients typically present with severe abdominal pain, there is increased likelihood that patients with acute porphyrias will be subjected to exploratory laparotomies, appendectomies, and/or cholecystectomies. Typically, at surgery there is no evidence of acute appendicitis or cholecystitis, and such surgeries do not relief or prevent recurrence of symptoms.

Type of anesthesia

General or regional anesthesia, both are possible under avoidance of triggering factors and unsafe or unclear medication.

Necessary additional preoperative testing (beside standard care)

- Consultation with an experienced anesthesiologist in advance to better plan surgery and anesthesia management.
- Consultation with a physician with special expertise in evaluation and management of porphyrias is desirable.
- Consultation with a neurologist if there are neurologic signs.
- Urine sampling (spot urine 20 ml, light protected) for preliminary staging of porphyrin precursors and porphyrins.

Particular preparation for airway management

None, only in special cases with known or suspected airway abnormalities.

Particular preparation for transfusion or administration of blood products

None.

Particular preparation for anticoagulation

None.

Particular precautions for positioning, transportation and mobilization

- Light protection and special yellow light filters for porphyria patients with light sensitivity.
- Soft positioning, gel cushion.

Interactions of chronic disease and anesthesia medications

No corticosteroids for initial PONV prophylaxis, induction medication: propofol (avoid barbiturates!), preoperative glucose supplementation. Strictly, avoid undernutrition.

Anesthetic procedure

- Preoperative preparation together with experienced anesthesiologist, surgeon or other physician with expertise in porphyria management.
- Obligate: Urine sampling (spot urine 20 ml, light protected) and laboratory values for preoperative staging of heme-precursors and porphyrins.
- Maintenance of fluid and carbohydrates (about 300 g/day). Start intravenous supplementation at the same time as preoperative fasting and maintain until return to adequate diet [9].
- Preparation in a stress-reduced setting with soft positioning.
- Premedication with midazolam if considered necessary [10].
- PONV prophylaxis: no corticosteroids, use droperidol [11, 12].
- Induction of anesthesia using opioids (morphine/fentanyl/remifentanil/sufentanil), propofol and vecuronium for relaxation, Maintenance using propofol or desflurane [11, 14].
- Use quantitative neuromuscular monitoring. Reversal of muscle relaxation, if necessary, with atropine/ neostigmine or sugammadex [11].
- Postoperative analgesia, morphine, paracetamol, ibuprofen or regional anesthesia technique using bupivacaine. Strictly avoid metamizole [11, 12].

Particular or additional monitoring

- Provide perioperative care, presurgical admission for iv hydration with glucose containing fluids (about 300 g/day) to avoid up-regulation of ALAS1 in liver.
- Intensify clinical monitoring (temperature, nausea, vomiting, diarrhea, seizures psychotic signs, peripheral neuropathy).
- Laboratory (serum sodium, color of urine, 5-ALA, porphobilinogen).
- Provide care on intermediate care or intensive care unit if necessary.

Possible complications

The disease may be disabling, but in most cases, it does not lead to a fatal outcome. Late diagnosis, however, and delayed onset of treatment may result in life-threatening complications like hyponatremia, tetra paresis, respiratory failure with the need of mechanical ventilation or in rare cases a lethal course [9].

In a life-threatening emergency situation, any necessary medication can be administered, even if that medication is or could be a porphyrinogen. Any induction of hepatic heme synthesis can be neutralized with heme (e.g., Normosang® or Panhematin®) [13].

A common symptom is abdominal pain. Together with symptoms like ileus, distention, constipation or diarrhea, nausea, vomiting it may be often misinterpreted as acute abdomen. Muscle weakness, sensory loss and peripheral neuropathy, due to axonal degeneration of neurons, mimicking GBS, may be seen. However, it is not common in all acute attacks;

progression up to respiratory or bulbar paralysis and death may occur if proper diagnosis and treatment are delayed.

Seizures are not uncommon due to hyponatremia, hypomagnesemia, or neurologic effects of porphyrin precursors. Treatment may be challenging because of exacerbation by most commonly used anticonvulsant drugs (barbiturates, hydantoins, lamotrigine, or other potent inducers of cytochromes P-450). Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Lorazepam, Midazolam, Propofol and Pregabalin are considered safe for use for treatment and prophylaxis of seizures complicating the acute porphyrias.

Postoperative care

- Provide sufficient perioperative care in the recovery room for all patients and provide additional care on Intermediate care or intensive care unit in extensive surgery.
- Continue iv. hydration with glucose containing fluids (about 300 g/day) to avoid increased synthesis of ALAS1 in liver.
- Provide heme intravenously (3 mg/kg BW per day for three to four days) if needed [Treatment of choice for acute porphyria attacks].
- Intensify monitoring for: hypothermia, psychotic symptoms, nausea, vomiting, diarrhea, seizures.
- Laboratory monitoring (serum sodium, magnesium levels, color of urine, 5-ALA, porphobilinogen).
- Avoid refeeding syndrome in malnourished patients (check phosphate in serum and glucose metabolism).

Disease-related acute problems and effect on anesthesia and recovery

In acute porphyria attacks: start acute crisis treatment with glucose and heme, in the form of heme arginate (Normosang®; Orphan Europe, Puteaux, France – in Europe and some other regions) or Panhematin®; Recordati Rare Diseases, Lebanon, NJ – in the United States, Mexico, and elsewhere).

In cases with unexplained gastrointestinal or neuropsychiatric symptoms: Be alert, these might be first signs of an acute attack. Consider relation to porphyria and start treatment with heme after diagnosis is biochemically confirmed.

Ambulatory anesthesia

It is recommended to not perform ambulatory anesthesia. As starvation must be avoided, pre- and postoperative supplementation of carbohydrates requires in-patient treatment.

Consultation with experienced anesthesiologist early in pregnancy to better plan surgery and procedures, examination, laboratory testing.

Determination of anesthesia type.

During delivery: sufficient pain therapy, early insertion of epidural catheter. If necessary, heme can be used in pregnancy [15].

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This recommendation was prepared in 2014 by:

Author(s)

Hans-Juergen Rapp, Anesthesiologist, Buergerhospital Frankfurt/Main, Germany
hj.rapp@buergerhospital-ffm.de

Disclosure: The author has no financial or other competing interest to disclose. This recommendation was unfunded.

This recommendation was reviewed by:

Reviewer(s)

Mike James, Anesthesiologist, University of Cape Town, South Africa
mike.james@uct.ac.za

Herbert Bonkovsky, Department of Medicine and The Liver-Biliary-Pancreatic Center, Carolinas Medical Center, Charlotte, North Carolina, USA
herbert.bonkovsky@carolinashealthcare.org

Disclosure: The reviewer(s) have no financial or other competing interest to disclose.

Update and revision (2026)

Ulrich Stölzel, Head of the Porphyria Center, Klinikum Chemnitz, Chemnitz, Germany
dr.stoelzel@porphyrie.de

Disclosure: The author has no financial or other competing interest to disclose. This recommendation was unfunded.

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Reviewer

Philipp Gude, Specialist in Anesthesia and Intensive Care Medicine,
Ruhr University Bochum, Bochum, Germany
St. Elisabeth-Hospital, Bochum, Germany
philipp.gude@kklbo.de

Disclosure: The reviewer is part of the OrphanAnesthesia project leadership. There are no financial or other competing interests to declare.

Editorial Review

Christine Gaik, Anesthesiologist, Department of Anesthesiology and Intensive Care Medicine, University Hospital Giessen and Marburg, Campus Marburg and Philipps University of Marburg, Germany
gaikc@med.uni-marburg.de

Appendix 1 – Prescription of drugs

Several lists of drugs have been developed over the past 40 years or so. All are based chiefly upon expert opinion and upon basic knowledge of the pharmacology of the drugs, such as whether drugs are known to be inducers of cytochromes P-450.

The main drugs lists are those of the Swedish Porphyria Centre, the Norwegian Porphyria Centre (NAPOS), the International Porphyria Initiative (Ipnet), the American Porphyria Foundation, and the South African/University of Capetown.

These lists have similar methods of classifying drugs and do not always agree. In these present "Anesthesia recommendation for porphyrias", we present the NAPOS list (https://drugsporphyria.net), which uses the following categories:

- Not porphyrinogenic (NP)
- Probably not porphyrinogenic (PNP)
- Possibly porphyrinogenic (PSP),
- Probably porphyrinogenic (PRP)
- Porphyrinogenic (P)
- Not yet classified (NC)

Select drugs accordingly: NP, PNP, PSP, PRP, P with first choice classified as NP or PNP.

Before prescribing any drug labeled PSP, PRP or P, it has to be justified:

- is there a real need for the drug?
- is there no safer alternative available?
- is there a benefit from using the drug of choice?
- is there a risk of provoking an acute attack and the consequences?
- Is the risk considered justified by the expected benefit?