# The Porphyrias

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## Opinion statement

- The porphyrias are a diverse group of metabolic diseases. Major manifestations are episodic neurovisceral attacks of pain or other neurologic features, and/or dermatologic abnormalities.
- It is essential that a clear diagnosis be established prior to planning management. In our experience, most patients referred with a presumptive diagnosis of "porphyria" do not have true porphyria at all, but rather have syndromes of other etiologies associated with mild, nonspecific increases in urinary porphyrin excretion (secondary porphyrinurias).
- The management of the acute or inducible porphyrias depends upon prevention and prompt, aggressive management of acute attacks. The latter includes nutrition (at least 300 g/d carbohydrate plus adequate [1–1.5 g/kg BW/d] protein), analgesia, and intravenous heme [3–4 mg/kg BW/d for 3-5 d].
- The management of active porphyria cutanea tarda involves iron depletion by therapeutic phlebotomy and cessation of precipitating or exacerbating factors, especially alcohol and estrogens. When chronic hepatitis C and/or HIV infection are present, they should also be treated.
- The management of protoporphyria involves ensuring adequate iron stores, and avoidance of hepatotoxic or cholestatic factors. Liver transplantation may be life-saving in the small minority of patients who develop progressive protoporphyric liver disease.
- A few patients with congential erythropoietic porphyria (Günther's disease) have been treated successfully by transplantation of bone marrow from a normal donor. In the future, this and other forms of porphyria may be treated by specific gene therapy. Such efforts are now under development, but they are not yet ready for human trials in the US.

## Introduction

The porphyrias are a group of metabolic diseases of heme synthesis in which there is a reduced activity in one of the eight enzymes needed for normal heme synthesis. When one of these enzymes is deficient, heme precursors may accumulate in the body, and cause symptoms. The determination of the exact type of porphyria requires careful integration of the history, physical exam, and laboratory studies on urine, feces, plasma, and red blood cell samples collected under specific conditions. Algorithms to facilitate the correct diagnosis have been presented. Care is also required to exclude secondary porphyrinurias caused by other conditions or drugs that are not true porphyrias but which may simulate them with mild abnormalities in urine or fecal porphyrins.

### CLASSIFICATION OF THE PORPHYRIAS

The porphyrias are classified in several ways:

**According to whether acute porphyric attacks can occur.** The acute or inducible porphyrias are delta-aminolevulinic acid dehydratase deficiency porphyria (ALAD-P), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). Those porphyrias in which acute porphyric attacks do not occur, are congenital erythropoietic porphyria (CEP), porphyria cutanea tarda (PCT), and hepato-erythropoietic porphyria (HEP). In another type of erythropoietic porphyria, namely EPP, acute attacks of neurologic dysfunction have occurred only very rarely and under the special circumstances of extremely ill patients with liver failure just prior to or after liver transplantation.

**According to the major site of excess production of porphyrins or their precursors.** These sites are hepatic (ALAD, AIP, PCT, HEP, HCP, VP) or erythropoietic (CEP, EPP). Thus, the chronic hepatic porphyrias with no acute attacks possible are PCT and HEP; the erythropoietic porphyria with no acute attacks possible is CEP.

**The major clinical categories with respect to treatment of an active porphyria** are usually divided into the acute/inducible porphyrias with neurovisceral symptoms (ALAD, AIP, HCP, and VP), or the chronic cutaneous porphyrias (CEP, PCT, HEP and EPP). In HCP and VP, both acute neurovisceral and chronic cutaneous symptoms may be present. All of the acute porphyrias may produce similar abrupt neurovisceral manifestations (severe, colicky abdominal pain, nausea, vomiting, motor neuropathy, sensory changes, CNS involvement, tachycardia, dark urine) and are treated similarly. Most of the cutaneous porphyrias present with vesicles, bullae, and skin fragility causing some degree of scarring, to the extent of mutilation in CEP and HEP. Hypertrichosis may be prominent in PCT. The skin manifestations of EPP are somewhat different and usually present in children as an intense burning pain in sun-exposed skin after brief sun exposure, followed after a few hours by erythema, edema, and itching. Chronically the skin may become hyperkeratotic and leathery.

### AIMS OF THERAPY

The aims of therapy are to relieve symptoms, and to remove or mobilize porphyrins or their precursors for excretion from the body. The general guidelines for treating an acute attack of porphyria are: to remove or treat precipitating factors (*eg*, drugs, infection, fasting, alcohol, stress of surgery); to administer safe medications for alleviating the major symptoms (*eg*, meperidine for pain, propranolol for tachycardia, chlorpromazine for nausea and agitation); and to provide counseling on measures to prevent future attacks in patients and susceptible relatives. Prevention is very important. MedicAlert bracelets and cards that specify the porphyria diagnosis and that indicate barbiturates, hydantoins, progestagens, and sulfonamides should be avoided should be carried by affected patients. Drugs that induce the cytochrome P450 system have the potential to precipitate acute porphyric attacks and should be avoided whenever possible. The general guidelines for treating the chronic porphyrias are avoidance of excessive sun exposure, and prompt treatment of secondary skin infections. Specific treatment options for the individual porphyrias are given below. The American Porphyria Foundation (P.O. Box 22712, Houston, TX 77227, tel: 713-266-9617; Internet: www.enterprise.net/apf) is a useful source of information for patients.

## Treatment: the acute porphyrias

- The acute porphyrias are ALA dehydratase deficiency, acute intermittent porphyria hereditary coproporphyria, and variegate porphyria.

### Diet and lifestyle

- Patients should consume a well-balanced, sensible diet with adequate carbohydrates and protein: 30–40 kCal/kg IBW/d; 1–1.5 g protein/kg IBW/d; 50%–60% of calories as complex carbohydrates, less than 30% of calories as fat.
- Advise patients to avoid fasting or severely hypocaloric diets; no “crash dieting.”
- Alcohol intake should be nil or modest (at most two drinks or less per day for men; one drink or less per day for women). Dark liquors are more porphyrogenic than light or clear liquors.
- Caution patients to avoid or minimize physical or psychological stress or exhaustion.
- Tell patients to avoid porphyrogenic drugs or chemicals.

## Pharmacologic treatment

- The aim of drug treatment is to provide symptomatic relief of the cardinal features of acute porphyric attacks, and to terminate the uncontrolled induction of ALA synthase by repleting the hepatic regulatory heme pool.
- For women with frequent cyclical attacks (usually occurring during the luteal phase of the menstrual cycle), prevention of endogenous cyclic progesterone production is often of benefit.

### *Analgesics*

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| **Standard dosage** | For mild to moderate pain: acetaminophen or aspirin 650–1000 mg every 4–6 hours, not to exceed 3000 mg/d. For severe pain: meperidine 100–200 mg IM every 4–6 hours; morphine $SO_4$, 3–12 mg IM every 4–6 hours. |
| **Contraindications** | Hypersensitivity to any of the drugs. |
| **Main drug interactions** | Analgesic and sedative effects are enhanced by concomitant phenothiazine. |
| **Main side effects** | Usual side effects of these types of analgesias. |
| **Special points** | Tramadol is to be avoided, because it is porphyrogenic [12]. |
| **Cost-effectiveness** | All these drugs are available as generic agents and are inexpensive compared to a day in the hospital. |

### *Anxiolytics: chlorpromazine*

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| **Standard dosage** | 10–50 mg PO or IM every 4–6 hours. |
| **Contraindications** | Hypersensitivity to the drug; hypotension. |
| **Main drug interactions** | Chlorpromazine will potentiate effects of opiate analgesics to decrease pain and blood pressure. |
| **Main side effects** | Excessive sedation, somnolence. |
| **Special points** | Chlorpromazine and other phenothiazines may cause cholestatic hepatitis. |
| **Cost-effectiveness** | Chlorpromazine is inexpensive, especially when administered orally. |

### *Nadolol or propranolol*

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| **Standard dosage** | For systemic arterial hypertension and/or tachycardia: 40–240 mg/d orally. |
| **Contraindications** | Hypersensitivity to either agent. |
| **Main drug interactions** | Will potentiate hypotensive effects of analgesics and/or phenothiazines. |
| **Main side effects** | Hypotension; bradycardia; coldness of the hands and feet; exacerbation of asthma or chronic obstructive pulmonary disease (COPD). |
| **Special points** | β-blockers must be used cautiously in patients with possible congestive heart failure, asthma, or COPD. |
| **Cost-effectiveness** | These drugs are available as inexpensive generic formulations. They are highly cost-effective, and we prefer them over newer brand-name drugs whose safety is less well-established. |

### *Heme (hematin) or heme arginate*

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| **Standard dosage** | For specific therapy to decrease hepatic ALA synthase: hematin (Panhematin, Abbot Laboratories Inc., North Chicago, IL) or heme arginate (available in Europe as Normosang, Leiras Medica, Helsinki, Finland), 3–5 mg heme/kg BW/d, given IV for 3–5 days. |
| **Contraindications** | Hypersensitivity to the drug. No hypersensitivity to Panhematin has been reported. One case of hypersensitivity to heme arginate has been observed in Japan in a women with AIP who was treated repeatedly over several years. She tolerated hematin without difficulty. |
| **Main drug interactions** | Infusions of heme have been reported to increase levels and activities of hepatic cytochrome P450 in both normal and acute poryphyric patients [1••]. The clinical significance of this is unknown. |

**Main side effects** Mild, transient decreases in platelet counts and anticoagulant effects: bleeding has occurred only in patients already receiving anticoagulants. Panhematin, especially if reconstituted in sterile water, has a high pH (~10), is irritating to veins, and often causes acute thrombophlebitis and venous thrombosis. These effects are diminished by reconstituting the lyophilized powder in human serum albumin (one vial Panhematin dissolved in 132 mL 25% HSA [1••].

**Special points** Panhematin is very unstable when the lyophilized powder is redissolved in water, and it must be administered immediately (complete infusion within 1 hr). It is stable when dissolved in HSA, and can be used or stored for at least 24 hours without loss of activity. Panhematin was the first orphan drug developed in the US. As of June 2000, there was a shortage of Panhematin in this country and pharmacies have had difficulty in obtaining it from Abbott Labs. Normosang is not appproved for use in the US, but is widely available in Europe and other regions.

**Cost-effectiveness** One vial of Panhematin costs hospital pharmacies about $300. However, the effectiveness of IV heme in acute porphyria more than justifies the cost.

### *Gonadotropin Releasing Hormone (GnRH) antagonists (leuprolide)*

**Standard dosage** First-line agents for prevention of cyclical attacks in women: 1 mg (0.2 mL) daily; 7.5 mg (1.0 mL) of Lupron Depot (TAP Pharmaceuticals, Deerfield, IL) monthly or 22.5 mg of Lupron Depot for 3 months.

**Contraindications** Hypersensitivity to leuprolide or any components of the drug preparation or dilutent (polylactic acid, D-mannitol, carboxymethyl cellulose, polysorbate 80).

**Main drug interactions** None known.

**Main side effects** Medical menopause: hot flashes, myalgias; headache; nausea, vomiting; acne; emotional lability; vaginitis.

**Special points** Has initial partial agonist effects and chronic antagonist effects. Therefore, the initial response may be an increase in estrogen and worsening of symptoms. Some patients require double the usual doses for full suppression of symptoms. Long-term therapy leads to osteoporosis, which should be treated prophylactically with 1.5–2.0 g calcium per day, assurance of adequate vitamin D levels, and perhaps bisphosphonates. Intranasal buserelin has recently become available and used in a porphyria patient.

**Cost-effectiveness** Moderately expensive, but worth the cost in patients who are suffering frequent cyclical attacks.

### *Low-dose oral contraceptives*

**Standard dosage** As a second-line agent: Norgestrel 0.3 mg, and ethinyl estradiol 0.03 mg (Lo/Ovral, Wyeth-Ayerst Laboratories, Philadelphia, PA) one tab PO per day.

**Contraindications** Concomitant cigarette smoking (much increased risk of thromboembolism); history of thromboembolism, hepatic adenoma or carcinoma, gallbladder disease; age greater than 35.

**Main drug interactions** Effectiveness diminished by inducers of cytochrome P450 (*eg,* phenobarbital, hydantoins, rifampin, phenylbutazone).

**Main side-effects** Nausea, vomiting, gastrointestinal pain and/or bloating, breakthrough bleeding.

**Special points** Estrogen and progesterone are porphyrogenic, and may increase symptoms of acute porphyria with initial use. The goal of therapy is to suppress endogenous cycles of GnRH and female sex hormones.

**Cost-effectiveness** Oral contraceptives are much less expensive (and easier to administer) than leuprolide. Intranasal buserelin, if consistently found effective and well-tolerated, will be easier for patients to take.

# Treatment: chronic cutaneous porphyrias

- The chronic cutaneous porphyrias consist of the following: congenital erythropoietic porphyria (CEP), porphyria cutanea tarda (PCT), hepatoerythropoietic porphyria (HEP), and erythropoietic protoporphyria (EPP).
- These porphyrias result from an accumulation of porphyrins in the skin, liver, and red cells, and the treatment goals include decreasing porphyrin overproduction, and enhancing their excretion.
- Important aspects include avoidance of strong sunlight, skin trauma, and secondary skin infection, and covering exposed areas with opaque sunscreens or clothing. The usual sunscreens are not very useful for blocking the long UV and visible wavelengths that elicit photosensitivity (380–420 nm). Topical zinc oxide or titanium dioxide block wavelengths of 380–650 nm, and can be used for temporary protection. Sunless tanning agents containing dihydroxyacetone may have limited benefit.

# Treatment: CEP (Günther's disease)

- CEP is rare, uroporphyrinogen III synthase is deficient, it is often diagnosed in infancy with red urine, erythrodontia, hemolytic anemia and blistering skin lesions with resultant scarring.

## Pharmacologic treatment

*Oral activated charcoal*

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| **Standard dosage** | A first-line agent, the optimal dose in adults is 30–100 g per day. A minimal dilution of 240 mL of water per 20 to 30 grams activated charcoal is recommended. |
| **Contraindications** | Gastrointestinal obstruction; unprotected airway in poorly responsive patients. |
| **Main drug interactions** | Can interfere with the absorption of many drugs. |
| **Main side effects** | May cause vomiting. Gastrointestinal obstruction has been reported. |
| **Special points** | Activated charcoal is not absorbed from the gastrointestinal tract. Different formulations may have different side-effects, including diarrhea and flatulence, an increased sodium load, or constipation necessitating lactulose. Very difficult for patients to use chronically, and few have done so. |
| **Cost-effectiveness** | About $1.70–$3.75 per day. Effective in some but not all CEP patients, and may be of benefit in patients with EPP to prevent the enterohepatic circulation of protoporphyrin. |

*Deferoxamine*

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| **Standard dosage** | For iron overload, the usual adult subcutaneous or intramuscular dose is 1–2 g daily. Each vial of Desferal Mesylate (Ciba-Geigy Corp., Summit, NJ) is reconstituted with 2 mL of sterile water to give 250 mg/mL, and each vial is protected from light. For subcutaneous administration, a daily dose of 1–2 g (20–40 mg/kg/d) infused over 8 to 24 hours, utilizing a small portable pump, is recommended. Administration of deferoxamine by subcutaneous bolus injection twice daily results in urinary iron excretion equal to that excreted after subcutaneous continuous infusion over 9–12 hours. Deferoxamine can be given IV with caution. |
| **Contraindications** | Severe renal disease. |
| **Main side effects** | Adverse effects include thrombocytopenia, hypotension, tachycardia, flushing, shock, retinal abnormalities, vision loss, tinnitus, hearing loss, and severe allergic reactions. Many of these complications occurred with IV administration. Neurotoxicity, superinfections have occurred. |

**Special points** To chelate iron that is subsequently excreted in the urine, agents must be administered parenterally.

**Cost-effectiveness** The cost of the desferoxamine is about $25 per g, however the costs of infusion are considerably higher.

### *Zinc oxide/titanium dioxide*

**Standard dosage** Apply twice a day (especially in the morning), may reapply hourly until desired coverage is attained. Can last more than day, depending upon washing or other removal; may stain clothing.

**Contraindications** Sensitivity to any of the components.

**Main side effects** For external use only. Avoid contact with eyes. Keep out of the reach of children. Discontinue use if signs of irritation or rash appear.

**Special points** To moisturize skin and protect it from harmful UVA and UVB rays. Main active ingredients for this use are zinc oxide and titanium dioxide. Preparations should be fragrance-free and non-comedogenic and hypoallergenic. Require repeated applications.

**Cost-effectiveness** These are relatively inexpensive and quite safe, but patients do not like having white opaque creams covering a lot of their skin surfaces.

### *Dihydroxyacetone*

**Standard dosage** 3.5% gel or topical lotion, apply to skin evenly, leave on 30 minutes and wash off.

**Contraindications** Hypersensitivity to dihydroxyacetone.

**Main drug interactions** None known.

**Main side effects** Rash; avoid contact with eyes and irritated skin.

**Special points** A component of "self-tanning" lotions, it binds to amino acids in the stratum corneum and results in an orange-brown color to the skin and blocks longer UVA and visible light. Also indicated for hypopigmentation, vitiligo.

**Cost-effectiveness** May have limited benefit in the chronic cutaneous porphyrias.

### *Glucocorticoids*

**Standard dosage** Prednisone 5–60 mg per day, individualized.

**Contraindications** Hypersensitivity, systemic fungal infections, may activate amebiasis, worsen cerebral malaria, should not receive smallpox vaccination, may worsen parasitic infections, TB, impair wound healing.

**Main side effects** Multiple, including anemia, leukocytosis, lymphopenia, thrombocytopenia, hypertensive crisis, hypertension, psychosis, schizophrenic psychosis, extrapyramidal effects, pseudotumor cerebri, hyperglycemia, hyperuricemia, hypercalcemia, adrenal suppression, Cushing's syndrome, lipid abnormalities, hypokalemia, peptic ulcers, pancreatitis, abdominal pain, nephrotoxicity, proteinuria, cataracts, papilledema, acne, osteonecrosis, osteoporosis, myopathy, and superinfections.

**Special points** Alternate day regimen may reduce Cushingoid side effects. A tapering regimen for withdrawing steroids may be required. Patients may be susceptible to adrenal insufficiency after withdrawing prednisone. Calcium and vitamin D replacement or alternatives may be required.

**Cost-effectiveness** Glucocorticoids may improve the anemia of CEP. Prednisone is not expensive; 20-mg tablets cost about $0.07 each.

### *Hydroxyurea*

**Standard dosage** Insufficient data on the usual dosage for this indication. Dose is individualized based on symptomatic and bone marrow response. Gradual increase from 2–8 g per week has been used [9].

**Contraindications** Hypersensitivity to hydroxyurea products; severe bone marrow depression.

**Main drug interactions** Live vaccines, rotavirus vaccine.

**Main side effects** Myelosuppression, thrombocytopenia, gastrointestinal disturbances, mutagenicity, rash, elevated liver tests and uric acid.

**Special points** An antineoplastic agent, it may be considered for use at puberty for patients with CEP. Not FDA-approved for this indication.

**Cost-effectiveness** Cost of hydroxyurea is $0.60–$6.30 per day; cost of repeated laboratory determinations adds to the expense.

## Transfusion

**Standard dosage** One pint, 450 mL of packed red cells.

**Contraindications** Inability to cross-match blood; fluid overload.

**Main side effects** Bruising, fever, transfusion reaction, low risk of transmission of infection, including hepatitis and human immunodeficiency virus.

**Special points** CEP patients with severe disease may be transfusion-dependent. Hyper-transfusion may benefit patients with EPP.

## Heme infusion

- See section on hematin infusion in the acute porphyrias section.

## Surgery

*Splenectomy*

**Standard procedure** Removal of the spleen at laparotomy or laparoscopy.

**Contraindications** Serious illness that precludes surgery.

**Main side effects** Susceptibility to infections from encapsulated organisms.

**Special points** Pneumococcal vaccination should be given at least 2 weeks before splenectomy.

**Cost-effectiveness** Used in severely affected patients in whom other less invasive therapies have not led to sufficient improvement.

## Allogeneic bone marrow transplantation

**Standard procedure** Ablation of host bone marrow and replacement with matched donor marrow.

**Contraindications** Other major organ failure, age at, about, or greater than 50 years, psychosocial factors, extrahepatic malignancy.

**Main side effects** Multiple, including requirement for suitable donor, increased risk of infection from immunosuppression, malignancy, diabetes mellitus, arterial hypertension, hepatic veno-occlusive disease, rejection, graft-versus host disease.

**Special points** Has been used for some patients with CEP.

**Cost-effectiveness** Expensive procedure as well as costly lifelong immunosuppression and medical follow-up.

## Other therapies

- The elevated levels of uroporphyrin and the symptoms of CEP may be reduced by large oral doses of activated charcoal in some CEP patients, by hyper-transfusion, or by infusions of heme. Severely affected patients may be transfusion dependent. Chronic transfusions to maintain a hematocrit over 35 suppress erythropoiesis and decrease porphyrin production, but long-term therapy is difficult and may lead to iron overload. Deferoxamine may reduce this iron overload.
- Large volumes of oral fluid may be helpful.
- Splenectomy can improve the hemolysis, and glucocorticoids may improve the anemia.

- Allogeneic bone marrow transplantation has cured some patients, and stem cell transplantation was performed on one patient with CEP.
- Hydroxyurea has been used to reduce bone marrow porphyrin synthesis around puberty, when porphyrin overproduction may increase.
- Protection of the skin from sunlight and minor trauma is most important, as is aggressive antibiotic treatment for skin trauma.

# Treatment: PCT

- PCT is the most common type of porphyria. In the more common sporadic (type I) PCT, reduced activity of uroporphyrinogen decarboxylase (UROD) is restricted to the liver, and there is no family history. In familial (type II) PCT a partial (50%) UROD deficiency is detectable in all tissues, but there is a low clinical penetrance. The 50% decrease in the activity of UROD in the inherited forms of PCT is not sufficient to produce clinical manifestations.
- Other factors, such as iron overload, chronic hepatitis C, alcohol abuse, estrogens, and porphyrogenic toxins, contribute to its manifestation.
- Alcohol, estrogens, and iron trigger or worsen PCT, and should be avoided. Patients should decrease intake of red meat, and avoid medicinal iron.
- Some environmental toxins may trigger PCT, *eg*, polyhalogenated biphenyls or dioxins.
- Although PCT is a chronic hepatic porphyria, it is safest for PCT patients to avoid barbiturates because they worsen experimental PCT-like porphyria.

## Pharmacologic therapy

*Antimalarial (first-line) agents*

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| **Standard dosage** | Chloroquine (Aralen Phosphate, Sterling Winthrop Inc., New York, NY) or hydroxychloroquine (Plaquenil Sulfate, Sterling Winthrop), 125 mg 2–3 times a week (low dose). Not FDA-approved. Dose adjustment is needed in renal and liver disease. |
| **Contraindications** | Hypersensitivity to 4-aminoquinoline products, retinal/visual field changes. Long-term use in children is contraindicated. |
| **Main drug interactions** | Interacts with aurothioglucose, cimetidine, cyclosporine, kaolin, magnesium compounds, praziquantel, rabies vaccine. |
| **Main side effects** | Methemoglobinemia, EKG changes, muscle weakness, hepatic injury. Dose adjustment is needed in renal and liver disease. For hydroxychloroquine: agranulocytosis, ocular toxicity, nausea, vomiting, skin and mucosal pigmentation, interacts additionally with digoxin. May favor progression of liver disease of PCT. |
| **Special points** | These agents form water-soluble complexes with uroporphyrin to facilitate its removal from the liver, other tissue store, and via urinary excretion. These agents must be started slowly and at low doses in PCT patients (125 mg 2–3 times a week) to reduce the chance of hepatic injury with fever, jaundice, and right upper quadrant pain. The dose may be gradually increased to 400–500 mg per day. Monitoring for possible retinal damage should be performed. Chloroquine usually produces clinical improvement in about 4 months. |
| **Cost-effectiveness** | The cost of chloroquine phosphate is $2.25–$31.50 per week, hydroxy-chloroquine sulphate is $0.80–$10.90 per week. Costs of laboratory and ophthalmology tests to monitor potential adverse effects are additional. |

*Deferoxamine*

See information on CEP and opinion statement for PCT, above.

### *Shohl's solution*

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| **Standard dosage** | Recommended dosages of Shohl's solution (sodium citrate and citric acid mix) are 15 to 30 mL after meals and at bedtime. One milliliter of the mixture provides one milli-equivalent of sodium bicarbonate. |
| **Contraindications** | Citrate salts are contraindicated in severe renal impairment with oliguria, azotemia, or anuria; Addison's disease; adynamic episodica hereditaria; acute dehydration; heat cramps; severe myocardial damage; hyperkalemia. |
| **Main side effects** | Use with caution in patients on sodium-restricted diets, those with congestive heart failure, pulmonary or peripheral edema, arterial hypertension, or toxemia of pregnancy, patients receiving blood products containing citrate, or those with acute liver failure. May cause hypocalcemia and metabolic alkalosis. Citrate salts may cause diarrhea, nausea and vomiting, reduced by taking after meals and diluting the mixture. Concurrent antacids should be avoided as they may cause aluminum toxicity (encephalopathy). Potassium may replace the sodium salts, but with different precautions. |
| **Special points** | For alkalinization of the urine to facilitate porphyrin excretion. |
| **Cost-effectiveness** | Cost of 15–30 mL 4x per day is about $0.70–$1.40 per day. |

### *Interferon*

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| **Standard dosage** | For treatment of concurrent chronic hepatitis C (if present): 3 million units SC 3 times per week for 1 year, depending upon response and viral genotype. |
| **Contraindications** | Sensitivity to its components. |
| **Main side effects** | Flu-like syndrome, fatigue, depression, loss of appetite, nausea/vomiting/diarrhea, thinning hair, itchy skin, thyroid problems, hematologic abnormalities. |
| **Special points** | Interferon has been used to treat the HCV infection commonly associated with PCT. Standard of care for treatment of chronic hepatitis C would currently include interferon plus ribavirin in a suitable patient, in order to give a higher viral and biochemical response rate. The side-effect profile of ribavirin is different from interferon and includes hemolysis. Should be administered by physicians with experience in their use. |
| **Cost-effectiveness** | Treatment is expensive, about $1200/month for combination therapy; maximal sustained response rates are about 40% in the US. Costs for monitoring potential adverse effects are additional. |

### *Erythropoietin*

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| **Standard dosage** | For inducing erythropoiesis: 50-100 U/kg IV/SC 3x/wk initial, 12.5–525 U/kg 3 times a week maintenance dose. |
| **Contraindications** | Uncontrolled arterial hypertension, hypersensitivity to albumin, hypersensitivity to mammalian cell-derived products. |
| **Main side effects** | Arterial hypertension, headaches, arthralgias. |
| **Special points** | Goal is to raise the hematocrit in PCT patients with renal insufficiency to permit phlebotomy for iron reduction. Erythropoietin 600 U/kg/wk has also been used in HEP. |
| **Cost-effectiveness** | About $360–$14,000 per week, depending on weight and dose. |

## Phlebotomy

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| | To remove heme and its iron to deplete iron stores in PCT. |
| **Standard dosage** | Initiate with 1 pint of blood per week to induce a mild anemia and decreased transferrin saturation. |
| **Contraindications** | Anemia (Hct < 30). Contraindicated in variegate porphyria. |
| **Main side effects** | Fatigue, infection, ecchymoses, fainting. |
| **Special points** | Venesection is effective even when hepatic iron stores are not increased. Skin improvements in PCT may not be visible for months. |

**Cost-effectiveness** An effective treatment, phlebotomy results in declining costs, which diminish markedly after initial iron depletion. Costs related to phlebotomy of one unit of blood are about $170.

### Plasmapheresis and charcoal hemoperfusion

In renal-failure patients with PCT who are undergoing hemodialysis, plasmapheresis may be the treatment of choice for the removal of plasma porphyrins. Alternatively, recombinant human erythropoietin stimulates iron mobilization and may raise the hematocrit to permit small volume venesection in these patients.

**Standard treatment** To remove plasma and serum porphyrins and their precursors. The required frequency is variable.

**Contraindications** Hypotension, inability to tolerate fluid shifts.

**Main side effects** Removes plasma proteins, sepsis, hemorrhage, anaphylaxis, hypotension.

**Special points** Used in hemodialysis patients with PCT and in patients with EPP who are awaiting liver transplant. Time consuming, requires invasive central venous catheters.

**Cost-effectiveness** Very expensive.

### Other therapies

- Iron depletion or low-dose chloroquine (Aralen) or hydroxychloroquine (Plaquenil) produce a prolonged remission in most patients. Removal of iron is the treatment of choice for patients with more severe disease. Deferoxamine chelation therapy (slow subcutaneous infusion) may be used instead of phlebotomy to remove hepatic iron stores.
- Treatment of co-existing hepatitis C, when present, is appropriate, some patients with PCT and chronic hepatitis C have experienced remission of PCT after interferon treatment alone, some without an associated viral clearance.
- PCT patients should be screened for the C282Y and H63D hemochromatosis HFE gene mutations, which are common in PCT [1].
- Alkalinization of the urine will increase urinary uroporphyrin excretion. Baking soda or Shohl's solution will achieve this.
- Promising results were observed in eight male PCT patients who were given thalidomide [13•]

## Treatment: EPP

- In EPP, ferrochelatase is deficient, and protoporphyrin accumulates.
- Intense, burning skin pain on brief sun exposure, and later skin edema and itching typifies protoporphyria. Chronic skin damage may occur, but is less severe than in PCT, CEP, or HEP. Protoporphyrin can only be removed from the body by biliary secretion from the liver.
- Cholecystectomy for symptomatic pigment gallstones in protoporphyria is appropriate in the absence of severe liver disease or other contraindications. Patients should have adequate iron stores.
- Drugs that can decrease bile flow may make EPP worse, *eg*, penicillins, erythromycins, estrogens, phenothiazines, excess alcohol (alcoholic hepatitis/cirrhosis).
- Patients with liver disease should avoid alcohol and be monitored frequently because decompensation can occur quickly.

- A liver biopsy should be performed for those with abnormal liver chemistries or very high red cell (>1500 μg/dL) or plasma (>150 μg/dL) protoporphyrin concentrations.
- Griseofulvin can cause experimental porphyria that resembles EPP, and should not be used in EPP patients.

## Pharmacologic treatment

### β–*Carotene*

Beta-carotene may ameliorate the photosensitivity of EPP, but a controlled trial did not show convincing benefit. Other antioxidants like vitamin E do not benefit protoporphyria patients, and beta-carotene probably does not help the photosensitivity seen with other porphyrias.

**Standard dosage** 120–180 mg per day with a recommended serum beta-carotene level of 600–800 μg/dL.

**Contraindications** Allergy to beta-carotene, lung cancer.

**Main side effects** Arthralgia, diarrhea, ecchymosis, yellowing of skin.

**Main drug interactions** Interacts with neomycin and orlistat (inhibits the absorption of carotene).

**Special points** A natural antioxidant carotenoid for EPP.

**Cost-effectiveness** The cost of 120–180 mg per day is $1.20–$1.80 per day, respectively.

### *Oral charcoal*

See section above on CEP.

## Resins: cholestyramine and colestipol

**Standard dosage** Resins include cholestyramine and colestipol. Dosage is 4–16 g/d in divided doses, taken with juice or water. In patients with an intact gallbladder, the morning dose should be ingested 30 min before and 30 min after breakfast.

**Contraindications** Complete biliary obstruction, hypersensitivity to resins.

**Main drug interactions** Should be taken 1 hr prior to, or 4–6 hr after other medications, as resins may decrease absorption of drugs. They may also decrease absorption of dietary lipids and fat soluble vitamins, necessitating replacement therapy. Absorption may be altered for thiazide diuretics, propranolol, tetracycline, penicillin G, phenobarbital, digitalis, thyroid supplements, estrogens, and progesterones.

**Main side effects** Mild transient constipation, flatulence, abdominal discomfort, anorexia.

**Special points** Resins bind protoporphyrin to prevent its enterohepatic circulation and promote its excretion.

**Cost-effectiveness** Cholestyramine is moderately expensive, 4–16 g daily costs $0.60–$2.40, bulk containers may be less expensive. Colestipol is used less frequently and is more expensive, daily costs $1.65–$4.95.

## Plasmapheresis

- See section on PCT.

## IV heme

- See section on acute porphyria attacks and hematin infusion.

## Surgery

*Liver transplantation*

| | |
|---|---|
| | Liver transplantation can be carried out for those with advanced liver disease and has been carried out in at least 15 EPP patients, but recurrent liver disease is a possibility since the ferrochelatase deficiency persists in the bone marrow. Combined liver and bone marrow transplantation should be considered. Plasmapheresis to reduce the pool of free protoporphyrin, followed by IV heme transfusions (3–5 mg/kg/d) to suppress heme biosynthesis, have given transient improvement while awaiting transplantation [14•]. |
| **Standard procedure** | Total hepatectomy and implantation of donor graft. |
| **Contraindications** | Other major organ failure, sepsis, advanced age, psychosocial factors, cholangiocarcinoma, extrahepatic malignancy. |
| **Main side effects** | Multiple, including increased risk of infection from immunosuppression, malignancy, diabetes mellitus, hyperlipidemia, arterial hypertension, bone disease. |
| **Special points** | For patients with liver failure from EPP. Does not correct the bone marrow deficit and EPP symptoms can recur. Timing can be difficult. Perioperative use of light filters (yellow, acrylate to minimize emission < 530 nm), and plasmapheresis are appropriate. In the absence of plasmapheresis preceding transplantation several patients have had severe and prolonged neuromuscular complications. |
| **Cost-effectiveness** | Expensive procedure as well as costly life-long immunosuppression and medical follow-up. Survival is comparable to other indications for liver transplantation. |

## Other therapies for various porphyrias

- HEP is rare and is often regarded as the homozygous or compound heterogygous form of type II PCT. UROD is decreased at least 75% in HEP. Infants have severe skin fragility and bullae, which results in deforming scarring.
- No treatment has been shown to be clearly effective; measures suggested for CEP may be tried. In contrast to PCT, there is no response to phlebotomy. Erythropoietin (600 U/kg/week) has been used for the severe anemia of HEP.
- Oral charcoal and cholestyramine decrease the enterohepatic circulation of protoporphyrin and may be beneficial.

## Emerging therapies

- Metalloporphyrins that inhibit heme oxygenase: a potential problem with intravenous heme therapies is that heme is a potent inducer of one form of heme oxygenase (HO-1), which is the rate-controlling enzyme of heme catabolism. Induction of HO-1 will limit the levels of heme attained and diminish its duration of action and perhaps its effectiveness. Therefore, a strategy that uses low doses of an inhibitor of HO and heme together is attractive [7,8•]. The most promising potent inhibitors of HO are tin- or zinc-mesoporphyrin.
- Gene therapy: some forms of erythropoietic porphyrias have already been treated successfully with bone marrow transplantation from a normal donor. Like other inborn errors of bone marrow development, the erythropoietic porphyrias should be ameliorated by insertion of normal genes into patients deficient in one of the steps of heme synthesis. Gene therapy in vitro in tissue culture has been accomplished for CEP and EPP.

## References and Recommended Reading

Recently published papers of particular interest have been highlighted as:
- • Of importance
- •• Of major importance


1.•• Bonkovsky HL, Healey JF, Lourie AN, Gerron GG: **Intravenous heme-albumin in acute intermittent porphyria. Evidence for repletion of hepatic hemoproteins and regulatory heme pools.** *Am J Gastroenterol* 1991, **86:**1050–1056.

A paper with details of how to prepare heme-albumin solutions, showing effectiveness of IV heme-albumin in acute porphyrias and effects in normal subjects.

2. Bonkovsky HL: **Advances in understanding and treating "the little imitator", acute porphyria.** *Gastroenterology* 1993, **105:**590–594.

3. Bonkovsky HL, Barnard GF: **Diagnosis of porphyric syndromes: a practical approach in the era of molecular biology.** *Semin Liver Dis* 1998, **18:**57–65.

Provides a cost-effective approach to diagnosis and differential diagnosis of the porphyrias, including charts of algorithms to follow.

4. Bonkovsky HL: **Porphyria cutanea tarda and hepatitis C.** *Viral Hepatitis Review 4* 1998:75–95.

A recent, comprehensive review.

5. Bonkovsky HL, Poh-Fitzpatrick M, Pimstone N, *et al.*: **Porphyria cutanea tarda, hepatitis C, and HFE gene mutations in North America.** *Hepatology* 1998, **27:**1661–1669.

Paper stressing the importance of risk factors (HCV infection, HFE mutations, alcohol, estrogens) in pathogenesis of clinically manifest PCT.

6. Bonkovsky HL, Barnard GF: The porphyrias. In *Conn's Current Therapy,* edn 52. Edited by Rakel RE. Philadelphia: WB Saunders; 2000:447–453.

An up-to-date review of pathogenesis and management.

7. Cable EE, Pepe JA, Karamitsios NC, *et al.*: **Differential effects of metalloporphyrins on mRNA levels of delta-aminolevulinate synthase and heme oxygenase: studies in cultured chick embryo liver cells.** *J Clin Invest* 1994, 649–654.

Paper establishing the principle of synergism of metalloporphyrins to down regulate ALA synthase.

8.• Dover SB, Moore MB, Fitzsimmons EJ, *et al.*: **Tin protoporphyrin prolongs the biochemical remission produced by heme arginate in acute hepatic porphyria.** *Gastroenterology* 1993, **105:**500–506.

First application in humans to the combination of heme plus an inhibitor of HO to prolong the therapeutic efficacy of heme in acute porphyria.

9. Guarini L, Piomelli S, Poh-Fitzpatrick MB, *et al.*: **Hydroxyurea in congenital erythropoietic porphyria.** *N Engl J Med* 1994, **330:**1092–1093.

10. Hahn M, Gildemeister OS, Krauss GL, *et al.*: **Effects of new anticonvulsant medications on porphyrin synthesis in cultured liver cells—potential implications for patients with acute porphyria.** *Neurology* 1997, **49:**97–106.

Demonstration of safety of gabapentin and vigabatrin, but not felbamate, lamotrigine, or tiagabine, among newer anticonvulsants.

11. Lambrecht RW, Gildemeister OS, Pepe JA, *et al.*: **Effects of antidepressants and benzodiazepine-type anxiolytic agents on hepatic porphyrin accumulation in primary cultures of chick embryo liver cells.** *J Pharmacol Exp Ther* 1999a, **29:**1150–1155.

Paper that defines which of the newer antidepressants and anxiolytic agents are safer for use in acute porphyria.

12. Lambrecht RW, Gildemeister OS, Williams A, *et al.*: **Effects of selected antihypertensives and analgesics on hepatic porphyrin accumulation.** *Biochem Pharmacol* 1999b, **58:**887–896.

Paper that defines which of the newer antihypertensive and analgesics are safer for use in acute porphyria.

13.• Monastrili A, Georgiou S, Bolsen K, *et al.*: **Treatment of porphyria cutanea tarda with oral thalidomide.** *Skin Pharmacol* 1999, **12:**305–311.

Recent interesting report; needs confirmation.

14.• Reichheld JH, Katz E, Banner BF, *et al.*: **The value of intravenous heme-albumin and plasmapheresis in reducing post-operative complications of orthotopic liver transplantation for erythropoietic protoporphyria.** *Transplantation* 1999, **67:**922–928.

Paper describing the usefulness of IV heme-albumin and plasmapheresis in managing EPP patients around the time of liver transplantation.