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# Update on the Porphyrias

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## Keywords

porphyria, acute hepatic porphyria, acute intermittent porphyria, protoporphyria, erythropoietic protoporphyria, porphyria cutanea tarda, congenital erythropoietic porphyria

## Abstract

The porphyrias are a group of rare diseases, each resulting from a defect in a different enzymatic step of the heme biosynthetic pathway. They can be broadly divided into two categories, hepatic and erythropoietic porphyrias, depending on the primary site of accumulation of heme intermediates. These disorders are multisystemic with variable symptoms that can be encountered by physicians in any specialty. Here, we review the porphyrias and describe their clinical presentation, diagnosis, and management. We discuss novel therapies that are approved or in development. Early diagnosis is key for the appropriate management and prevention of long-term complications in these rare disorders.

## INTRODUCTION

The porphyrias are a group of rare diseases, each resulting from enzymatic defects of heme synthesis (1). These can be divided into hepatic and erythropoietic porphyrias, depending on the primary site of accumulation of heme intermediates (2). The porphyrias can also be classified clinically as acute hepatic (AHP) and cutaneous, with the latter category being further divided into blistering and nonblistering (3). The eight porphyrias are acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), δ-aminolevulinic acid dehydratase (ALAD) deficiency porphyria (ADP), erythropoietic protoporphyria (EPP), X-linked protoporphyria (XLP), porphyria cutanea tarda (PCT), and congenital erythropoietic porphyria (CEP) (**Figure 1**). These are inherited in an autosomal dominant, recessive, or X-linked pattern, except for PCT, which can be sporadic or acquired (2, 4).

In porphyria, decreased or increased enzymatic function results in the accumulation of heme precursors or porphyrins. The specific accumulated intermediates and the site of accumulation are responsible for the distinct clinical features of each type of porphyria (1). Due to variable clinical presentations and decreased awareness of these disorders, long diagnostic delays are common (5). This often leads to chronic complications, significant disease burden, and decreased quality of life (6).

Recent advances in our understanding of the porphyrias have led to the development of novel targeted therapies, dramatically transforming patient care (2). In this review, we aim to discuss the current state of diagnosis and treatment of the acute and cutaneous porphyrias.

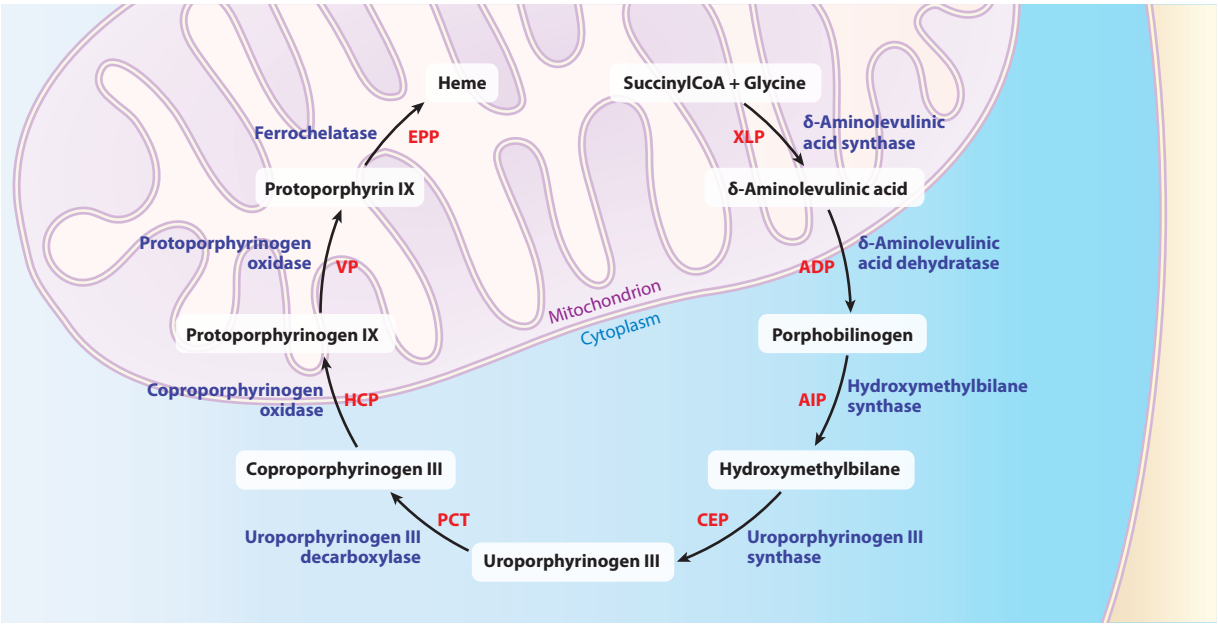


**Figure 1**

Heme biosynthesis and porphyria. Abbreviations (clockwise from top right): XLP, X-linked protoporphyria (gain of function in δ-aminolevulinic acid synthase 2); ADP, δ-aminolevulinic acid dehydratase deficiency porphyria; AIP, acute intermittent porphyria; CEP, congenital erythropoietic porphyria; PCT, porphyria cutanea tarda; HCP, hereditary coproporphyria; VP, variegate porphyria; EPP, erythropoietic protoporphyria.

## ACUTE HEPATIC PORPHYRIA

The AHPs include AIP, VP, HCP, and ADP (7). The first three are inherited in an autosomal dominant fashion with low penetrance, while ADP is an ultrarare recessive disorder. These disorders result from pathogenic genetic variants in hydroxymethylbilane synthase (HMBS), protoporphyrinogen oxidase (PPOX), coproporphyrinogen oxidase (CPOX), and ALAD, respectively. Patients with AHP can develop acute neurovisceral attacks often characterized by abdominal pain, nausea, vomiting, and other neurologic and psychiatric symptoms such as weakness, numbness, paresthesias, seizures, anxiety, depression, or psychosis (7). In VP and HCP, patients may have acute neurovisceral attacks, blistering cutaneous photosensitivity, or both, with cutaneous symptoms occurring more frequently in VP than in HCP (8).

In addition to acute attacks, AHP patients, particularly those with recurrent attacks, can have chronic symptoms and long-term complications such as chronic pain, neuropathy, liver disease, and kidney disease (7).

### Epidemiology and Genetics

Studies suggest that the prevalence of AIP is ~0.5–2:100,000; however, analysis of genetic data sets shows that the prevalence of pathogenic variants in HMBS is ~1:1700, suggesting lower penetrance than previously thought (9, 10) (**Table 1**). These data suggest that the penetrance may be <1% depending on the degree of underdiagnosis (9). However, the penetrance is 10–20% among family members of symptomatic AIP patients (10–12). VP and HCP are less common, with the prevalence of diagnosed VP being ~0.3:100,000 and the prevalence of diagnosed HCP being ~0.1:100,000 (10) (**Table 1**). Founder variants exist in Scandinavia for AIP and in South Africa for VP, leading to a higher prevalence of these diseases in those regions (13, 14). ADP is ultrarare, with less than 10 cases reported, all in males (15). Except for ADP, most symptomatic AHP patients are females, as hormones, particularly progesterone, contribute to the onset of attacks and disease activity (10, 16). However, other reasons for differences in disease presentation in individuals with pathogenic variants are poorly understood (9). Misdiagnosis is common, with patients in the United States experiencing an average of 15 years of diagnostic delay (7).

### Pathophysiology

Delta-aminolevulinate synthase 1 (ALAS1) is the first and rate-limiting step in heme biosynthesis and is highly inducible. Factors that directly increase ALAS1 transcription or increase heme

**Table 1 Prevalence of the porphyrias**

| Type of porphyria | Prevalence |
|---|---|
| Acute intermittent porphyria | ~0.5–2:100,000 (9, 10) |
| Variegate porphyria | ~0.3:100,000 (10) |
| Hereditary coproporphyria | ~0.1:100,000 (10) |
| ALAD deficiency porphyria | <10 cases reported, all in males (15) |
| Erythropoietic protoporphyria | 1:100,000 diagnosed, true prevalence as high as 1:17,000 (10, 42) |
| X-linked protoporphyria | Up to 10% of protoporphyria (40) |
| Porphyria cutanea tarda | 1:25,000 in the United States (80, 81) |
| Congenital erythropoietic porphryia | ~1:1,000,000, around 200 cases reported worldwide (88) |

Abbreviation: ALAD, δ-aminolevulinic acid dehydratase.

demand can upregulate ALAS1. With the increase in ALAS1 activity, the enzymatic deficiencies cannot keep up with this increased demand for heme, creating a block in the pathway and leading to the accumulation of porphyrins and porphyrin precursors. The pathogenesis of AHP symptoms is attributed to the accumulation of the toxic metabolites δ-aminolevulinic acid (ALA) and porphobilinogen (PBG), particularly ALA (17). Factors that influence the activity of ALAS1 and induce AHP attacks include stress, alcohol, smoking, medications, caloric restriction, acute illnesses, and the luteal phase of the menstrual cycle (17–20). These affect ALAS1 activity either by directly increasing transcription (e.g., dieting or fasting) or increasing hepatic heme demand or consumption (e.g., drugs, illness) (17, 19). Therefore, fasting and heme deficiency can precipitate attacks (17, 19, 21).

## Diagnosis

Clinicians should have a low threshold to screen for AHP, especially in women in the reproductive age group with unexplained, recurrent abdominal pain without a clear etiology or nonspecific neurologic symptoms, including neuropathy and weakness (3, 22). The diagnostic test for AHP includes assessing PBG and ALA in a spot urine sample (22) (**Table 2**). Urine porphyrin levels should not be used in isolation for screening or diagnosis. Significant elevation in urine PBG is highly specific for AHP, but elevations in urine porphyrins are neither specific nor diagnostic (23). Urine porphyrins can be elevated in liver disease, in heavy metal poisoning, and in the setting of the use of a variety of medications (23). Spot testing with normalization to urine creatinine is recommended, and 24-h testing is unnecessary, with the potential to cause delays in diagnosis (22, 24). Although urine PBG and ALA are elevated in attacks of AIP, VP, and HCP, in ADP only urine ALA and porphyrins are elevated due to the underlying enzymatic defect (15).

Testing during acute symptoms is important because the urine PBG may be normal between attacks, leading to the potential for a missed diagnosis (22, 23). Compared with AIP, the urine PBG may be more transiently elevated in VP and HCP. Second-line testing should be pursued if testing for AHP is positive or inconclusive (23). This includes testing urine, fecal, and plasma porphyrins. Stool porphyrins are often elevated in VP and HCP, with stool coproporphyrin being particularly elevated in HCP and stool protoporphyrin and coproporphyrin being particularly elevated in VP (23). Plasma porphyrins may be elevated in AHP, especially in the setting of cutaneous symptoms in VP and HCP. While urine ALA is elevated in acute attacks of porphyria, this is less specific for

**Table 2 Symptoms and key diagnostic testing for the porphyrias**

| Type of porphyria | Symptoms | Key diagnostic test |
|---|---|---|
| ***Acute hepatic*** | | |
| AIP, VP, HCP, ADP | Acute pain attacks and/or other neurovisceral symptoms, blistering lesions on sun-exposed skin (VP, HCP) | Urine PBG[a] and ALA[b] |
| ***Cutaneous*** | | |
| Blistering (PCT, CEP, VP, HCP) | Blistering lesions on sun-exposed skin | Plasma and urine porphyrins[a] |
| Nonblistering (EPP, XLP) | Painful light sensitivity that is typically nonblistering | Erythrocyte protoporphyrin[c] |

Abbreviations: ADP, δ-aminolevulinic acid dehydratase deficiency porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; CEP, congenital erythropoietic porphyria; EPP, erythropoietic protoporphyria; HCP, hereditary coproporphyria; PBG, porphobilinogen; PCT, porphyria cutanea tarda; VP, variegate porphyria; XLP, X-linked protoporphyria.

[a] Random spot urine samples are recommended over 24-h values; however, concurrent urine creatinine must also be collected.

[b] Urine PBG may not be elevated in ADP, though ALA will be markedly elevated.

[c] Including total protoporphyrin and quantification of metal-free and zinc fractions.

AHP than PBG elevation. For patients with AIP, the measurement of HMBS has been used in the past; however, the expected activity ranges for individuals with and without AIP have overlapping values, decreasing the usefulness of this test (23). Genetic testing is useful to confirm the diagnosis, determine the subtype of porphyria, and test at-risk family members. Genetic testing is available clinically as part of multigene panels.

## Natural History

Patients with acute porphyria may develop autonomic neuropathy, peripheral neuropathy, and/or central nervous system dysfunction (25). The autonomic neuropathy in AHP causes diffuse, severe abdominal pain, tachycardia, hypertension, constipation, nausea, and vomiting. Peripheral neuropathy can be profound and progressive, resulting in paresthesias and/or weakness, including respiratory muscle weakness. The central nervous system dysfunction leads to insomnia, anxiety, depression, hallucinations, cognitive dysfunction, and/or seizures. Other common symptoms during attacks include hyponatremia, dark or red urine, and fatigue (18–20). The most common of these symptoms are abdominal pain, fatigue, nausea, dark or red urine, and weakness (18, 24).

Studies show that about 60% of symptomatic patients with AIP will develop chronic kidney disease, and the risk is lower in patients with elevated porphyrin precursors without overt clinical symptoms compared to those with symptoms. AHP patients are also at risk of liver disease and hepatocellular carcinoma (HCC) (18, 26, 27). The risk of HCC increases with age, and it typically occurs in noncirrhotic livers (28). Studies from Europe suggest an annual incidence of 1.8% in AHP patients who have had previous elevations of urine PBG (29). A US study found HCC in 1.5% of AHP patients including asymptomatic carriers (28).

The disease severity and pattern of symptoms in AHP vary widely among patients. A vast majority of HMBS pathogenic variant carriers will remain latent with no clinical symptoms and normal biochemical testing (9, 11, 12). Asymptomatic high excretors are defined as patients with no history of recent acute attacks but with elevations in urine PBG ~4 times the upper limit of normal. Some patients have one or a few attacks throughout their lifetime, classified as sporadic attacks (18). A subset of patients have recurrent attacks (≥4 per year) and also report chronic symptoms between attacks (6). Survey studies reveal remarkable impairments in quality of life, which are similar for those with and without recurrent attacks (6).

## Clinical Management

The management of symptoms should focus on avoiding triggering or precipitating factors (22). Patients should be counseled extensively on the use of safe medications and the avoidance of unsafe medications, fasting, dieting, alcohol, tobacco, and other factors that may precipitate symptoms (22).

**Management of acute attacks.** Acute attacks that require hospitalization should be treated with intravenous hemin (21, 30) (**Table 3**). Ideally, an elevated urine PBG level should be determined before hemin administration, but patients with a confirmed AHP diagnosis should receive hemin based on their symptoms, as waiting for results may lead to delays in therapy. Hemin mixed in 25% albumin rather than sterile water is more stable and less likely to cause phlebitis (31). Typically, patients receive 3–4 mg/kg daily over 4 days, a regimen that decreases symptoms and urine PBG, although neurologic improvement may lag (21, 24). Hemin works by repleting the free heme pool in the liver, which downregulates ALAS1 and thereby decreases the production of the neurotoxic heme precursors ALA and PBG (31). Intravenous dextrose may also prove useful in downregulating ALAS1 (22, 24). Pain should be managed aggressively with analgesics, and patients may require antiemetics for nausea. Hypertension, tachycardia, and hyponatremia are common,

**Table 3 Available therapies and therapies under development for porphyria**

| Type of porphyria | Therapies in use[a] | Potential therapies in clinical trials | Therapies in development |
|---|---|---|---|
| ***Acute hepatic*** | | | |
| AIP | Panhematin (21), givosiran (37) | None | Gene therapy (93), intravenous administration of PBGD mRNA (94) |
| VP | Panhematin (21)[b], givosiran (37) | None | None |
| HCP | Panhematin (21, 30)[b], givosiran (37) | None | None |
| ADP | Panhematin (21, 95)[b,c] | None | None |
| ***Blistering cutaneous*** | | | |
| PCT | Therapeutic phlebotomy (86), hydroxychloroquine (85), hepatitis C antiviral therapy (87) | None | None |
| CEP | Blood transfusion (88), therapeutic phlebotomy (90), iron chelation (96) | None | Ciclopirox (92) |
| ***Nonblistering cutaneous*** | | | |
| EPP | Afamelanotide (55) | Dersimelagon (59), bitopertin (60), cimetidine (61) | Antisense oligonucleotides (97), inhibition of ABCG2 transporter (98) |
| XLP | Afamelanotide (55) | Dersimelagon (59), cimetidine (61) | None |

Abbreviations: ADP, δ-aminolevulinic acid dehydratase deficiency porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; CEP, congenital erythropoietic porphyria; EPP, erythropoietic protoporphyria; HCP, hereditary coproporphyria; PBGD, porphobilinogen deaminase; PCT, porphyria cutanea tarda; VP, variegate porphyria; XLP, X-linked protoporphyria.

[a]For details on liver and bone marrow transplant in the porphyrias, please see text.

[b]Panhematin is not approved for treatment of VP, HCP, or ADP but is used off-label.

[c]In case reports, givosiran has not been shown to be beneficial in ADP (99).

and electrolytes should be carefully monitored and repleted. Patients should be monitored for neurologic complications, including seizures.

**Prevention of attacks.** Hemin has been used prophylactically off-label in AHP patients with recurrent attacks to prevent attacks and hospitalization (32). Long-term hemin use can be associated with complications, including iron overload and phlebitis. Other therapies, including GnRH (gonadotropin-releasing hormone) analogs, have been used in women with cyclic attacks related to their menstrual cycle, with mixed results (33). While liver transplantation is curative in AHP, this is generally only considered in individuals with severely debilitating symptoms not responsive to other pharmacologic measures (34, 35). Both liver and kidney transplantation have been reported in AHP cases with end-stage renal disease. In a report from France, kidney transplantation in patients with AIP and end-stage renal disease significantly reduced AIP disease activity (36).

Givosiran, a small interfering RNA (siRNA) targeting ALAS1 in hepatocytes, is approved by the US Food and Drug Administration for treating adults with AHP (**Table 3**). It is administered subcutaneously at 2.5 mg/kg monthly to prevent attacks. In a pivotal phase III clinical trial, givosiran decreased the annualized attack rate by 74% compared to the placebo group (37). It was associated with reduced urine ALA and PBG and improved quality of life. Patients on givosiran experienced an improvement in chronic symptoms and a decrease in hemin and pain medication

usage. The side effects include increased liver biochemistries, decreased eGFR (estimated glomerular filtration rate), and increased homocysteine levels (37, 38). Patients on givosiran should be monitored closely after treatment initiation with clinical and laboratory assessments, including the measurement of liver enzymes, kidney function, homocysteine, amylase, and lipase (27). Givosiran should not be used in women who are pregnant or planning to become pregnant, as limited safety data exist.

No therapies are known to treat the blistering photosensitivity seen in VP and HCP, besides sunlight avoidance and sun-protective clothing. Givosiran's role in treating the skin symptoms of VP and HCP is unclear.

**Long-term monitoring.** Patients should be monitored annually with assessments of hepatic and kidney function (27). In patients with persistent liver enzyme elevations, other etiologies should be considered and ruled out. Up to 59% of symptomatic AIP cases have porphyria-associated kidney disease (22). In AHP patients with porphyria-associated kidney disease and concomitant chronic hypertension, medical management and monitoring are important to prevent additional kidney damage (22). AHP patients over age 50 should have surveillance by liver ultrasounds every 6 months, regardless of clinical symptoms, to monitor for HCC (27).

## ERYTHROPOIETIC PROTOPORPHYRIA AND X-LINKED PORPHYRIA

EPP and XLP are rare photodermatoses characterized by severe painful cutaneous phototoxicity after light exposure. Patients with EPP have pathogenic variants of ferrochelatase (*FECH*), the last enzyme of heme synthesis. EPP is recessive, and more than 95% of patients have a pathogenic variant on one allele and a common *FECH c.315–48T>C* low-expression variant on the other (39–41). The *FECH c.315–48T>C* variant has a prevalence of 10% in the Caucasian population and around 50% in East Asians (42).

Up to 10% of individuals with protoporphyria will be found to have XLP upon molecular testing (40). While EPP is caused by loss-of-function variants in *FECH*, patients with XLP have gain-of-function pathogenic variants in the erythroid-specific *ALAS2*, which encodes the first enzyme of heme synthesis (43, 44). Females with XLP may present with a clinically variable phenotype ranging from asymptomatic to equally symptomatic as males based on X chromosome inactivation (43, 44). Protoporphyria due to a pathogenic variant of another gene, *ClpX*, has been identified in one family (45). In about 4% of cases with the protoporphyria phenotype, no pathogenic variants have been identified in these genes. The prevalence of protoporphyria was previously thought to be about 1:100,000; however, analysis of genetic data sets suggests that EPP may be as common as 1:17,000 due to underdiagnosis (10, 42) (**Table 1**).

### Diagnosis

In both EPP and XLP, total erythrocyte protoporphyrin that is predominantly metal-free accumulates in erythroid cells and secondarily in the plasma and bile (46). Due to the deficiency of FECH, which inserts iron into the protoporphyrin IX tetrapyrrole to form heme, the percentage of protoporphyrin that is metal-free in EPP is >85%, with the remainder being complexed to zinc (40). In XLP, on the other hand, the zinc fraction is typically 50–85% (40, 43). Protoporphyria is diagnosed by a measurement of total erythrocyte protoporphyrin that is more than 3–4 times normal and predominantly metal-free (47) (**Table 2**). Notably, many laboratories offer a "free erythrocyte protoporphyrin" ("FEP") test that only measures zinc erythrocyte protoporphyrin, and use of such testing could miss a diagnosis of protoporphyria, as zinc erythrocyte protoporphyrin may be normal in protoporphyria (46). The United Porphyrias Association and the European Porphyria Network websites provide lists of acceptable laboratories for protoporphyria testing. Genetic

testing is useful both to confirm the diagnosis and to differentiate between EPP and XLP. Because ~4% of patients with protoporphyria have cryptic or unknown variants, negative genetic testing does not rule out the disease (40, 47). While plasma porphyrins are often elevated in protoporphyria, plasma, stool, and urine porphyrins may all be normal, so these should not be used to establish a diagnosis (48).

## Clinical Presentation

Phototoxic symptoms in EPP and XLP are indistinguishable. In both, protoporphyrin absorbs energy from light and damages the endothelium and subcutaneous tissues through a process that involves the production of reactive oxygen species (49, 50). After light exposure, patients experience a prodrome of tingling and itching that can progress to severe burning pain and allodynia, which can last for days (51, 52). Pain is often associated with nonpitting edema and sometimes petechiae, and the most sensitive skin regions are the hands, face, and feet (51).

Because patients are sensitive to the blue region of visible light and not primary UV light, broad-spectrum or tinted sunscreen might have a small benefit, but other sunscreens are ineffective (47). Light avoidance and light-protective clothing are needed to prevent symptoms, which impair quality of life (53, 54). Afamelanotide was approved in the United States in 2019 to prevent phototoxic symptoms in protoporphyria (55–58) (**Table 3**). It is an α-melanocyte stimulating hormone (α-MSH) agonist administered as a subcutaneous implant every 2 months. This medication increases eumelanin and decreases light-mediated protoporphyrin activation through its antioxidant effect (58).

Clinical trials are underway for new therapies for protoporphyria (59, 60) (**Table 3**). These include dersimelagon, an orally administered small-peptide α-MSH agonist currently in a phase III extension study (59). In a phase II clinical trial, dersimelagon-treated patients had a clinically significant increase in the time to first prodromal symptoms compared to placebo. Additionally, a phase II clinical trial is underway for bitopertin, which is a potential disease-modifying therapy that inhibits the uptake of glycine into erythroid cells (60). A phase II clinical trial for cimetidine for protoporphyria is also ongoing (61).

## Anemia and Iron Deficiency

Patients with protoporphyria have an increased risk of anemia and iron deficiency, which is poorly understood (62–67). Soluble transferrin receptor levels in protoporphyria patients suggest that hematopoiesis in protoporphyria may not truly be iron restricted, and supplementing iron has been observed to increase protoporphyrin in EPP patients, at least transiently (64, 65, 68–70). Current recommendations are to consider supplemental iron in EPP patients who are symptomatic and/or have both hemoglobin <10 g/dL and ferritin <10 μg/L (47). Because supplemental iron in the setting of normal FECH activity is thought to be beneficial to potential heme formation, iron supplementation for iron deficiency in XLP is recommended (47, 71). Due to the risk of anemia in protoporphyria, hemoglobin and iron studies should be monitored at least yearly (47).

## Liver Dysfunction

Because protoporphyrin is hydrophobic, it is excreted in the bile of protoporphyria patients—not in the urine, as in other porphyrias. This can lead to liver dysfunction in a subset of protoporphyria patients. While ~27% of patients may have elevated liver biochemistries, approximately 2–4% develop liver failure due to the toxic effects of protoporphyrin on the liver (72). Protoporphyric hepatopathy is characterized by protoporphyrin deposition in the liver, particularly the characteristic Maltese-cross inclusions visible with polarized light (73, 74). In the context of liver failure

in protoporphyria, protoporphyrin levels can rise substantially, potentiating damage to the liver (73). Therapies such as plasmapheresis may be able to temporize the protoporphyrin-mediated liver damage, but progression to liver failure and liver transplantation are expected (75, 76). In protoporphyria, bone marrow transplantation is curative and is typically performed after liver transplantation to prevent recurrence in the transplanted liver (77, 78). Patients with protoporphyria and progressive protoporphyric hepatopathy should be cared for by a hepatologist with experience in managing protoporphyria-related liver disease and at a liver transplant center (47).

Total erythrocyte protoporphyrin levels, plasma porphyrin levels, and liver biochemistries should be monitored at least yearly, and a hepatologist should evaluate any abnormalities in liver biochemistries (47). Patients should be vaccinated against hepatitis A and B and advised to avoid excessive alcohol intake (79).

## PORPHYRIA CUTANEA TARDA

PCT is thought to be the most common type of porphyria, with an estimated prevalence of 1:25,000 in the United States (80, 81) (**Table 1**). While variants of uroporphyrinogen decarboxylase (*UROD*), found in 17% of US patients, can predispose to disease, there are many other risk factors (4, 82). Variants in *UROD* are neither necessary nor sufficient for developing PCT. Therefore, while the other types of porphyria are inherited, PCT is considered an acquired condition.

Besides pathogenic variants of *UROD*, other risk factors for PCT include viral hepatitis, alcohol consumption, tobacco use, estrogen use, hemochromatosis, and HIV (4). In the United States, these risk factors are found in 69%, 87%, 81%, 66%, 53%, and 13% of patients, respectively; however, the prevalence of risk factors among PCT patients varies highly by country (82). Most patients with PCT will have at least two risk factors, which collectively decrease patients' hepatic UROD activity to <50% (80, 82). The end result is an increase in hepatic iron, which produces functional inhibition of the UROD enzyme, possibly through the production of an oxidized porphyrin that inhibits UROD (83).

In PCT, the accumulated porphyrins are photoactivated by light, producing skin fragility and blistering (82). Patients may also develop hypertrichosis and scarring. However, unlike in protoporphyria, skin symptoms in PCT are often not painful (51, 81, 82). The cutaneous signs and symptoms in VP and HCP and late-onset CEP can be identical to PCT (81, 84).

PCT is diagnosed by urine or plasma porphyrins (**Table 2**). Either will demonstrate marked elevations of porphyrins that are many-fold normal, and elevations of uroporphyrin are especially prominent (80, 81). Risk factors such as UROD variants, variants consistent with hemochromatosis, use of estrogens, smoking, alcohol, and positive HIV status should also be assessed during the work-up. While a skin biopsy can support the diagnosis of PCT, this is not sufficient for diagnosis, as identical pathology can be observed in pseudoporphyria, which can be idiopathic or due to various medications (81, 82). PCT can be distinguished from the cutaneous symptoms of variegate porphyria and hereditary coproporphyria through genetic testing (48, 81). Moreover, PCT can be distinguished from late-onset congenital erythropoietic porphyria through genetic testing or the measurement of erythrocyte porphyrins, which are elevated in CEP but not PCT (84).

PCT can be effectively treated with phlebotomy or low-dose hydroxychloroquine (85, 86) (**Table 3**). Phlebotomy decreases serum porphyrins and reduces iron overload by removing blood from the body, while low-dose hydroxychloroquine promotes the excretion of porphyrins through the urine. In PCT patients with hepatitis C, PCT can be effectively treated by addressing hepatitis C alone using direct-acting antivirals (87). Urine porphyrins, plasma porphyrins, ferritin, iron studies, and complete blood count should be monitored during therapy, and urine porphyrins and plasma porphyrins should be measured at least yearly thereafter to monitor for recurrence.

## CONGENITAL ERYTHROPOIETIC PORPHYRIA

CEP is a rare type of porphyria with an estimated prevalence of 1:1,000,000, with ~200 cases reported total worldwide (88) (**Table 1**). CEP is recessively inherited, with patients possessing two pathogenic variants of uroporphyrinogen synthase (88). It has also been described in one patient with a pathogenic variant of a GATA-1 erythrocyte-specific transcription factor on the X chromosome (89). CEP results in the accumulation of porphyrins in erythrocytes. This produces blistering and skin fragility beginning in infancy, which can be highly disfiguring and can result in auto-amputation (88). Patients may have fluorescent erythrodontia, red fluorescent urine, corneal ulcers, thrombocytopenia, and transfusion-dependent anemia (88). For those who are not anemic, phlebotomy can help decrease erythrocyte porphyrins and minimize symptoms (90) (**Table 3**). There may also be a role for iron chelation therapy in CEP (91) (**Table 3**). Bone marrow transplantation is curative in CEP and is beneficial for those who are transfusion dependent or who have disfiguring symptoms (88). The disease severity can vary greatly, ranging from hydrops fetalis to adult-onset forms restricted to mild cutaneous photosensitivity (84, 88). Outside of phlebotomy, iron chelation, and bone marrow transplantation, the management of cutaneous symptoms in CEP currently centers on sunlight avoidance and sun-protective clothing. A clinical trial for CEP is planned to test the efficacy of ciclopirox, which has been shown to stabilize the uroporphyrinogen synthase enzyme (92) (**Table 3**).

## CONCLUSION

The porphyrias are a diverse group of rare diseases characterized by alterations in the heme biosynthetic pathway. They are multisystemic disorders, and physicians of essentially every specialty have the potential to encounter these patients. While more research is needed to better understand the pathophysiology of the porphyrias and to develop effective disease-modifying treatments, the currently approved therapies and those in clinical development provide great hope to the porphyria community.

## DISCLOSURE STATEMENT

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