Received: 23 December 2023 | Revised: 4 May 2024 | Accepted: 7 May 2024

DOI: 10.1111/liv.15980

Liver INTERNATIONAL WILEY

REVIEW

The clinical management of porphyria cutanea tarda: An update

R. P. E. Sarkany[1] | J. D. Phillips[2]

[1]Photobiology and Cutaneous Porphyria Unit, St. John's Institute of Dermatology, London, UK

[2]Division of Hematology, University of Utah, Salt Lake City, Utah, USA

Correspondence
R. P. E. Sarkany, Photobiology and Cutaneous Porphyria Unit, St. John's Institute of Dermatology, London, UK.
Email: robert.sarkany@gstt.nhs.uk

Handling Editor: Luca Valenti

Abstract

Porphyria cutanea tarda (PCT) is the commonest of the porphyrias (*Semin Liver Dis* 1998;18:67). It often occurs secondary to an underlying internal disorder, has significant impacts on liver health and longevity, and is a treatable disease. Thus, for the clinician, recognising the disease to make the correct diagnosis, identifying causative underlying diseases, and treating the porphyria and its complications, are crucial. Although reviews on the management of PCT have been written, there have recently been significant advances in the understanding of the factors predisposing to the disease, and of its wider health impacts. This review aims to help the clinician to diagnose and manage patients with PCT, with an emphasis on the impact of recent advances on clinical management.

KEYWORDS
hemochromatosis, hepatitis C, PCT, porphyria, uroporphyrin

1 | MAKING THE DIAGNOSIS OF PCT

1.1 | Clinical presentation

Sporadic PCT (S-PCT), the non-genetically based form, usually presents in middle age whilst Familial PCT (F-PCT) can occur at a younger age.[1] Patients present with fragility of the skin on the backs of the hands and, less commonly, the face. This may be accompanied by the formation of thick-roofed painful blisters, which are haemorrhagic or filled with clear fluid. Despite the role of light in the pathogenesis of the skin disease, patients usually give no history of photosensitivity, though they may notice aggravation of symptoms in the summer months or after sunny holidays.

The findings on examination of the skin are often confined to the backs of the hands, with thick roofed, haemorrhagic or clear fluid-filled bullae, erosions, patchy pigmentation, scarring and the presence of small milial cysts (Figure 1). Less common presentations include: painful onycholysis, hypertrichosis on the face (which may mimic hirsutism), facial pigmentation sometimes in a melasma-like pattern on cheeks and forehead. It may cause morphoea-like indurated plaques, frequently in non-exposed areas such as the chest wall.[2] Rarer presentations include lichenoid eruptions,[3,4] hair darkening,[5] or transient bouts of painful immediate photosensitivity.[6]

There is a wide clinical differential diagnosis. Two conditions commonly present with clinical features indistinguishable from the skin of PCT patients: variegate porphyria and pseudoporphyria. Variegate porphyria (VP) generally presents during adolescence. It is critical not to miss the diagnosis of VP because of the importance of avoiding triggers of acute attacks, and of carrying out genetic testing in family members, in this disease. Pseudoporphyria usually presents with skin features identical to PCT and variegate porphyria. It is generally due to drug phototoxicity, associated with haemodialysis or a complication of addiction to sunbathing.[7]

Although there are many dermatological conditions which cause skin fragility and blistering, most occur in a different distribution. The exception is fragility due to chronic ultraviolet radiation-induced damage, which involves the backs of the hands. However, it can be differentiated because it does not cause bulla formation, usually also

involves the forearms, and is associated with other signs of chronic actinic damage.

Typical histological appearances of PCT in the skin are of cell infiltrate-poor bullae whose cleavage plane is in the upper dermis or lower part of the basement membrane (lamina lucida). There is characteristic festooning of dermal papillae into the bulla's cavity. Hyaline material is deposited around upper dermal blood vessels. Electron microscopy shows upper dermal vacuole formation related to cell lysis and extracellular matrix damage.[8]

1.2 | Diagnostic investigations

Where there is a clinical suspicion that a patient has PCT, the diagnostic tests are porphyrin assays.

The biochemical defect which causes PCT is partial deficiency of the fifth enzyme in the haem synthesis pathway, uroporphyrinogen decarboxylase (UROD).[9] This results in defective decarboxylation of uroporphyrinogen III, leading to accumulation of uroporphyrinogen III and its partially decarboxylated intermediates hepta-, hexa- and pentacarboxylic acid porphyrinogens. These intermediates are easily oxidised from the porphyrinogen to the corresponding porphyrin. The more highly carboxylated porphyrins are water soluble, allowing them to be filtered and excreted in the urine. Intermediates with fewer carboxyl groups, pentacarboxylporphyrin and coproporphyrin become insoluble in water and are excreted in the faeces. High-Performance Liquid Chromatography (HPLC) is able to separate the accumulated urine porphyrins as uroporphyrin III, hepta-, hexa-, pentacarboxylic acid porphyrins and coproporphyrin.[10] The diagnosis of PCT is confirmed by the additional findings of a 615–620 nm peak on plasma porphyrin fluorimetry, or of isocoproporphyrin on HPLC of faeces. This is important because occasionally variegate porphyria causes a urine porphyrin pattern which is similar to that of PCT ('dual porphyria'),[11,12] creating the danger that porphyrin analysis in urine alone by the inexperienced may lead to the misdiagnosis of variegate porphyria as PCT.

Key points

- Porphyria cutanea tarda (PCT) is the commonest of the porphyrias.
- Unlike other porphyrias, acquired factors play a significant role in the pathogenesis of PCT.
- Inhibition of uroporphyrinogen decarboxylase (UROD) in the liver plays the key role in pathogenesis of PCT.
- Haemochromatosis, hepatitis C, alcohol, oral oestrogens, HIV and UROD mutations are the major predisposing factors.
- Therapy involves elimination of predisposing factors, venesection or low dose oral chloroquine or hydropxychloroquine.

2 | PATHOGENESIS AND PREDISPOSING CAUSES

Approximately 25% of PCT cases are attributed to *type II* PCT (F-PCT) with a hereditary enzyme deficiency in all tissues caused by a mutation in one allele of the UROD gene. The penetrance of this autosomal dominant defect is low: there is a family history in under 7% of patients. F-PCT is an autosomal dominant disease with incomplete penetrance indicating that other factors are necessary for expression of the PCT phenotype. These additional risk factors contribute to an oxidising environment within the hepatocyte further reducing the activity of UROD. UROD mutations may be considered as another risk factor for PCT, rather than a separate familial form of the disease. The remaining 75% of patients have *type I* (S-PCT), in

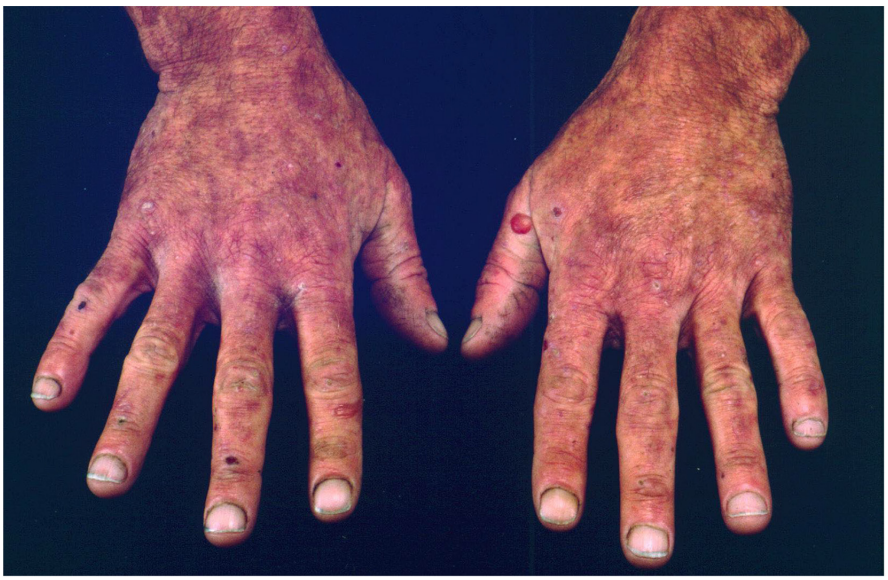

FIGURE 1 Typical clinical features in PCT. The photograph shows: typical site (dorsum of hands), haemorrhagic bullae, erosions, milia, well demarcated pigmentation, scarring.

which the normal hepatocyte UROD enzyme is inhibited to approximately 20% of normal. The inhibition is caused by an uroporphomethene, a partially oxidised substrate that is produced as a result of the oxidation of one of the bridge carbons of uroporphyrinogen (Figure 2).[13] In all cases of PCT, the activity of UROD in hepatocytes is significantly decreased to approximately 20% of normal.

Production of the uroporphomethene inhibitor is more likely in hepatocytes undergoing oxidative stress and containing plentiful iron.[14] Hence, diseases which create hepatocyte oxidative stress or iron accumulation predispose to PCT, and most patients have an underlying predisposing hepatic or internal disorder.[15]

The key risk factors for PCT are: excess alcohol consumption, haemochromatosis, hepatitis C and HIV infection, and exogenous oestrogens.[15]

Heavy alcohol consumption (>40 g/day) occurs in 60%–90% of patients with PCT.[15] Hepatitis C infection is also strongly linked, the proportion of patients carrying the infection varying geographically according to the population prevalence of the viral infection: from as low as 10% in Ireland[16] to 59% in the USA[17] and 82% in Italy.[18] Although there is an association between human immunodeficiency virus (HIV) infection and PCT,[19] this may be due to co-infection with hepatitis C rather than being a direct effect of the HIV virus itself.[20] Haemochromatosis, with homozygosity for the Cys282Tyr mutation, is found in 20% of PCT patients in Northern Europe and the USA,[17,21] though it is a less significant risk factor in Southern Europe where hepatitis C is so important. Exogenous oral oestrogens, usually Hormone Replacement Therapy, are the sole risk factor in around a quarter of female patients.[17]

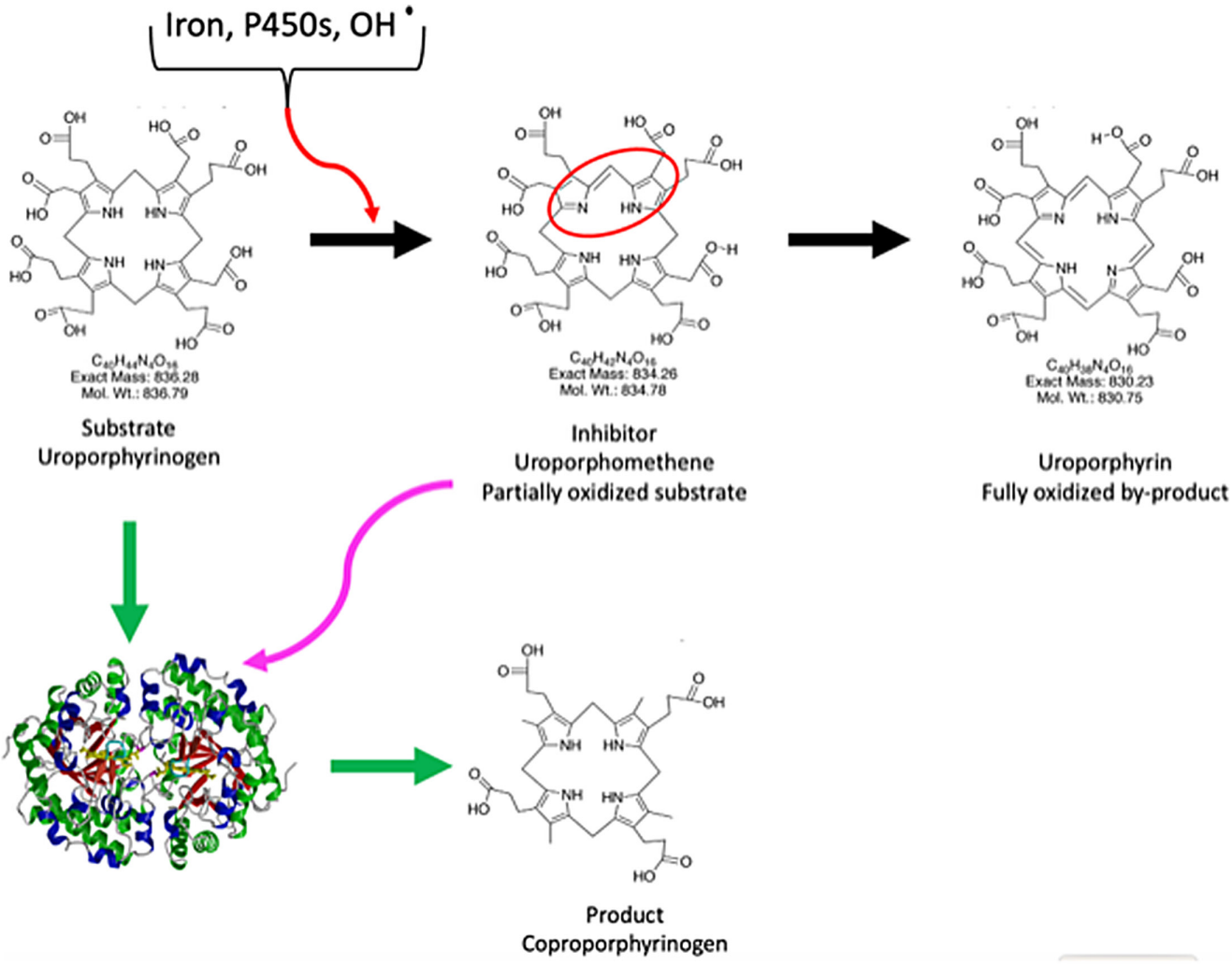

FIGURE 2 The pathogenesis of hepatic UROD deficiency in PCT begins with the partial oxidation of the substrate uroporphyrinogen (structure 1). Oxidation of a single bridge carbon (in the red circle) reduces the flexibility of the substrate and creates a suicide inhibitor of the enzyme (pink arrow). The substrate can be fully oxidised to uroporphyrin (black arrows) and excreted in the urine. The normal pathway is for uroporphyrinogen to be decarboxylated at each of the four acetate groups to the product coproporphyrinogen, then further metabolised to make heme. The presence of excess iron (Fenton chemistry), hydroxyl radical, and excessive cytochrome P450 activity increases the oxidising environment and converts more substrate to inhibitor.

Generally patients have more than one risk factor: in one study, 92% of patients with PCT had 3 or more risk factors.[22]

It is vital to take a detailed history from patients for risk factors, and clinicians should routinely test patients for haemochromatosis, hepatitis C and HIV infection. In our experience, haemochromatosis is particularly important to test for because patients are usually not aware that they have this disease in which early diagnosis can be lifesaving.

3 | THERAPY

Effective treatment exists for PCT. This is important partly because the skin symptoms can be debilitating. It is also likely that the poor health outcomes of PCT patients might be improved by good long-term control of the porphyria (see below under 'PCT and lifespan').

3.1 | Elimination of underlying risk factors

This can be very effective. Eradication of hepatitis C infection with antiviral medications (ribavirin, boceprevir, etc.) is curative for the porphyria in all patients.[23] Women taking oral oestrogens in hormone replacement therapy (HRT) do not have to stop HRT. Instead it can be changed from the oral to the patch formulation which avoids first-pass metabolism of exogenous oestrogens in the liver.[24] Where excessive alcohol is a factor, reducing consumption can be effective, but alcohol abuse is frequently a persistent and recurrent problem.

3.2 | Photoprotection

While porphyrin levels remain high, there is no substitute for photoprotection to reduce phototoxic damage to the skin. This can be perplexing for patients who are unaware of a link with sun exposure. Reducing daylight and sunlight exposure to the hands and face involves wearing gloves and broad written brimmed hats and practising avoidance behaviour. The peak pathogenic wavelength for excitation of porphyrins is 408 nm (exciting waveband 400–420 nm), so standard ultraviolet sunscreen creams that block UVB and UVA (290–400 nm) are of no value. However, recent technological advances have led to the development of sunscreens protective into the visible range, which may provide good protection against the pathogenic short wavelength blue light (400–420 nm), and so may be of value in PCT.[25]

3.3 | Specific treatments

Low-dose oral antimalarials and venesection are both effective in PCT.

Low-dose antimalarial medications (hydroxychloroquine 100 mg or 200 mg twice weekly, or chloroquine 125 or 250 mg twice weekly) increase urinary excretion of uroporphyrin. While the mechanism has not been fully determined, it is likely that the quinol changes the pH of the lysosomal compartment, where the excess porphyrins are stored within hepatocytes, allowing the accumulated porphyrins to be transported out of the cell into the plasma and eventually cleared by the kidney into the urine.[26] It is crucial to avoid taking these drugs at the (higher) doses at which they are prescribed for malaria or lupus: in PCT this can cause a potentially dangerous acute hepatitis. Chloroquine or hydroxychloroquine at low dose are both effective in most patients, leading to clinical remission within 6 months and biochemical remission after 6–15 months (at which point the treatment is stopped).[27–30]

Regular venesection aiming to induce mild iron deficiency is effective, presumably working by altering iron homeostasis and creating iron depletion within hepatocytes. It is useful for patients in whom antimalarial drugs are contraindicated or ineffective, and for those who have haemochromatosis. With venesection, blistering generally resolves after 2–3 months, and skin fragility within around 6–9 months.[31] Porphyrin concentrations normalise within a year or so.[32]

A small number of patients are resistant to all of these treatments. In this situation, venesection and low dose antimalarials may be combined.

In patients who develop PCT as a result of renal failure, venesection and low dose antimalarials are usually contraindicated. Erythropoietin is an effective alternative means of mobilising iron from the liver, and can be effective in this situation.[33] For the many patients in renal failure already on erythropoietin, the dose can be increased to treat the porphyria. If this induces polycythaemia, this can be resolved by discarding blood during haemodialysis.

4 | PCT AND LIFESPAN

Two recent studies have shown an unexpectedly large reduction in lifespan in patients with PCT.

In a recent large study in Denmark in which patients were matched with healthy population controls, the survival rate in the PCT group after 25 years was around 50% lower than that in the healthy controls[34] (Figure 3).

Another large nationwide cohort study in Norway has recently explored the causes of the reduced lifespan of PCT patients. The PCT patients were predisposed to hepatocellular carcinoma and biliary tract cancer compared to healthy adults (adjusted hazard ratios (aHRs): 19.7 for hepatocellular carcinoma and 6.8 for biliary tract cancer). Even after adjusting these hazard ratios for alcohol intake, by matching cases and controls by alcohol intake, PCT was still associated with increased hazard ratios for these diseases (3.1 for hepatocellular carcinoma and 4.0 for biliary tract cancers). Compared to the reference population, PCT patients had an increased risk of premature death (aHR 1.5) due to malignancies (hazard ratio = 1.4), liver disease (hazard ratio = 5.5), and drug and alcohol overdose (hazard ratio = 9.9).[35]

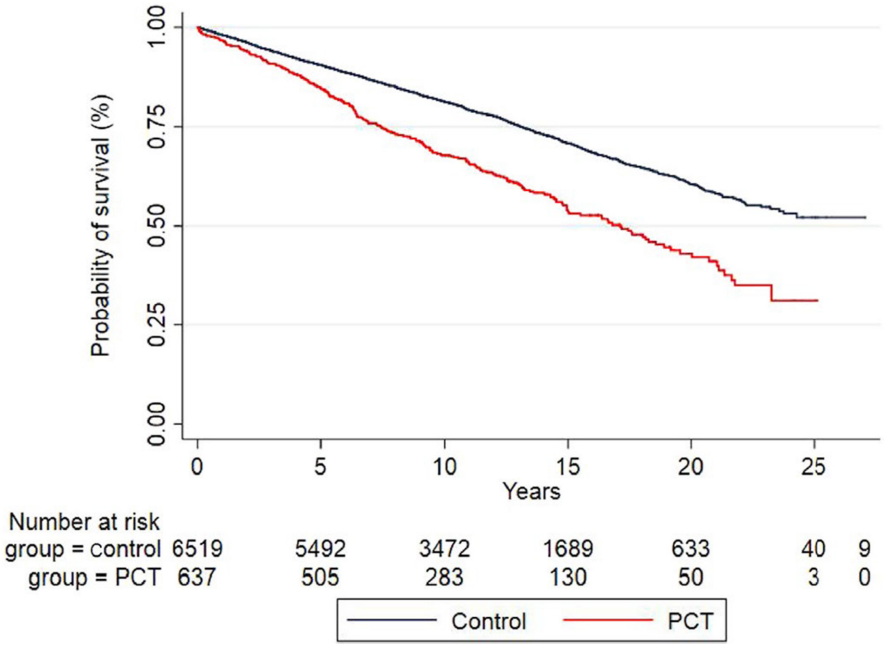

FIGURE 3 Kaplan–Meier curve in PCT patients in Denmark compared to matched controls from the general population, showing reduced lifespan in PCT. Reproduced with permission from reference 34.

5 | CONCLUSION

PCT is a relatively common disease. Early diagnosis and management are critical in order to treat the debilitating skin disease, and to identify and treat underlying internal causes. The recent finding of a dramatic shortening of lifespan in PCT emphasises the importance of diagnosing and treating this disorder and its causes.

CONFLICT OF INTEREST STATEMENT

The authors do not have any disclosures to report.

ORCID

J. D. Phillips https://orcid.org/0000-0003-1567-1678

REFERENCES

1. Sarkany RPE. The management of porphyria cutanea tarda. *Clin Exp Dermatol*. 2001;26:225-232.
2. Grossman ME, Bickers DR, Poh-Fitzpatrick MB, Deleo VA, Harber LC. Porphyria cutanea tarda: clinical features and laboratory findings in 40 patients. *Am J Med*. 1979;67:277-286.
3. Toussi A, le ST, Merleev AA, et al. Porphyria cutanea tarda presenting as a lichenoid eruption. *Photodermatol Photoimmunol Photomed*. 2021;37:233-235.
4. Creamer D, Mcgregor JM, Mcfadden J, Hawk JL. Lichenoid tissue reaction in porphyria cutanea tarda. *Br J Dermatol*. 1999;141:123-126.
5. Shaffrali FC, McDonagh AJ, Messenger AG. Hair darkening in porphyria cutanea tarda. *Br J Dermatol*. 2002;146:325-329.
6. Dawe RS, Clark C, Ferguson J. Porphyria cutanea tarda presenting as solar urticaria. *Br J Dermatol*. 1999;141:590-591.
7. Sarkany RPE. The cutaneous porphyrias. In: Griffiths C, Barker J, Bleiker TO, Hussain W, Simpson RC, eds. *Rook's Textbook of Dermatology*. 10th ed. Wiley Blackwell; 2024:58.1-58.20.
8. Caputo R, Berti E, Gasparini G, Monti M. The morphologic events of blister formation in porphyria cutanea tarda. *Int J Dermatol*. 1983;22:467-472.
9. Elder GH, Urquhart AJ, De Salamanca RE, et al. Immunoreactive uroporphyrinogen decarboxylase in the liver in porphyria cutanea tarda. *Lancet*. 1985;2:229-233.
10. Elder GH. Porphyria cutanea tarda. *Semin Liver Dis*. 1998;18:67-75.
11. Sturrock ED, Meissner PN, Maeder DL, Kirsch RE. Uroporphyrinogen decarboxylase and protoporphyrinogen oxidase in dual porphyria. *S Afr Med J*. 1989;76:405-408.
12. Sieg I, Bhutani LK, Doss MO. Dual porphyria of coexisting variegata and cutanea tarda. *Eur J Clin Chem Clin Biochem*. 1995;33:405-410.
13. Phillips JD, Bergonia HA, Reilly CA, Franklin MR, Kushner JP. A porphomethene inhibitor of uroporphyrinogen decarboxylase causes porphyria cutanea tarda. *Proc Natl Acad Sci USA*. 2007;104:5079-5084.
14. Elder GH. Alcohol intake and porphyria cutanea tarda. *Clin Dermatol*. 1999;17:431-436.
15. Singal AK. Porphyria cutanea tarda: recent update. *Mol Genet Metab*. 2019;128:271-281.
16. Murphy A, Dooley S, Hillary IB, Murphy GM. HCV infection in porphyria cutanea tarda. *Lancet*. 1993;341:1534-1535.
17. Bulaj ZJ, Phillips JD, Ajioka RS, et al. Hemochromatosis genes and other factors contributing to the pathogenesis of porphyria cutanea tarda. *Blood*. 2000;95:1565-1571.
18. Fargion S, Piperno A, Cappellini MD, et al. Hepatitis C virus and porphyria cutanea tarda: evidence of a strong association. *Hepatology*. 1992;16:1322-1326.
19. Blauvelt A, Ross Harris H, Hogan DJ, et al. Porphyria cutanea tarda and human immunodeficiency virus infection. *Int J Dermatol*. 1992;31:474-479.
20. Aguilera P, Laguno M, To-Figueras J. Human immunodeficiency virus and risk of porphyria cutanea tarda: a possible association examined in a large hospital. *Photodermatol Photoimmunol Photomed*. 2016;32:93-97.
21. Roberts AG, Whatley SD, Morgan RR, Worwood M, Elder GH. Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria cutanea tarda. *Lancet*. 1997;349:321-323.
22. Egger NG, Goeger DE, Payne DA, Miskovsky EP, Weinman SA, Anderson KE. Porphyria cutanea tarda: multiplicity of risk factors including HFE mutations, hepatitis C, and inherited uroporphyrinogen decarboxylase deficiency. *Dig Dis Sci*. 2002;47:419-426.

23. Combalia A, To Figueras J, Laguno M, et al. Direct-acting antivirals for hepatitis C virus induce a rapid clinical and biochemical remission of porphyria cutanea tarda. *Br J Dermatol*. 2017;177:e183-e184.
24. Bulaj ZJ, Franklin MR, Phillips JD, et al. Transdermal estrogen replacement therapy in postmenopausal women previously treated for porphyria cutanea tarda. *J Lab Clin Med*. 2000;136:482-488.
25. Eadie E, Josso M, Touti R, Renoux P, Dawe RS, Ibbotson SH. Commercial visible-light protecting sunscreens for photosensitive individuals. *Br J Dermatol*. 2023;188:445-447.
26. Scholnick PL, Epstein J, Marver HS. The molecular basis of the action of chloroquine in porphyria cutanea tarda. *J Invest Dermatol*. 1973;61:226-232.
27. Malina L, Chlumsky J. A comparative study of the results of phlebotomy therapy and low-dose chloroquine treatment in porphyria cutanea tarda. *Acta Derm Venereol Suppl (Stockh)*. 1981;61:346-350.
28. Ashton RE, Hawk JLM, Magnus IA. Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. *Br J Dermatol*. 1984;111:609-613.
29. Valls V, Ena J, Enriquez-de-Salamanca R. Low-dose oral chloroquine in patients with porphyria cutanea tarda and low-moderate iron overload. *J Dermatol Sci*. 1994;7:164-175.
30. Singal AK, Kormos-Hallberg C, Lee C, et al. Low-dose hydroxychloroquine is as effective as phlebotomy in treatment of patients with porphyria cutanea tarda. *Clin Gastroenterol Hepatol*. 2012;10:1402-1409.
31. Wennersten G, Ros A-M. Chloroquine in treatment of porphyria cutanea tarda. Long-term efficacy of combined phlebotomy and high-dose chloroquine therapy. *Acta Derm Venereol Suppl (Stockh)*. 1982;100:119-123.
32. Mascaro JM, Herrero C, Lecha M, et al. Uroporphyrinogen-decarboxylase deficiencies: porphyria cutanea tarda and related conditions. *Semin Dermatol*. 1986;5:115-124.
33. Sarkell B, Patterson JW. Treatment of porphyria cutanea tarda of end-stage renal disease with erythropoietin. *J Am Acad Dermatol*. 1993;29:499-500.
34. Christiansen AL, Brock A, Bygum A, Rasmussen LM, Jepsen P. Increased mortality in patients with porphyria cutanea tarda-a nationwide cohort study. *J Am Acad Dermatol*. 2020;83:817-823.
35. Baravelli CM, Sandberg S, Aarsand AK, Tollånes MC. Porphyria cutanea tarda increases risk of hepatocellular carcinoma and premature death: a nationwide cohort study. *Orphanet J Rare Dis*. 2019;14:77-86.

How to cite this article: Sarkany RPE, Phillips JD. The clinical management of porphyria cutanea tarda: An update. *Liver Int*. 2024;44:2191-2196. doi:10.1111/liv.15980