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Evidence-based consensus guidelines for the diagnosis and management of erythropoietic protoporphyria and X-linked protoporphyria

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Abstract

Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are rare genetic photodermatoses. Limited expertise with these disorders among physicians leads to diagnostic delays. Here, we present evidence-based consensus guidelines for the diagnosis, monitoring, and management of EPP and XLP. A systematic literature review was conducted, and reviewed among sub-committees of experts, divided by topic. Consensus on guidelines was reached within each sub-committee and then among all members of the committee. The appropriate biochemical and genetic testing to establish the diagnosis is reviewed in addition to the interpretation of results. Prevention of symptoms, management of acute phototoxicity, and pharmacologic and non-pharmacologic treatment options are discussed. The importance of ongoing monitoring for liver disease, iron deficiency, and vitamin D deficiency is discussed with management guidance. Finally, management of pregnancy, surgery, and the safety of other therapies are summarized. We emphasize that these are multisystemic disorders that require longitudinal monitoring. These guidelines provide a structure for evidence-based diagnosis and management for practicing physicians. Early diagnosis and management of these disorders are essential, particularly given the availability of new and emerging therapies.

Keywords

erythropoietic protoporphyria; X-linked protoporphyria; protoporphyria; EPP; XLP; guidelines; evidence-based; consensus; diagnosis; management; cutaneous porphyria; photodermatoses

Introduction

Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are rare genetic disorders of the heme biosynthetic pathway characterized by the accumulation of

protoporphyrin in erythrocytes, plasma, and the biliary system.[1] Although indistinguishable clinically, EPP results from loss-of-function variants in ferrochelatase (FECH), the last enzyme of heme biosynthesis, and XLP results from gain-of-function variants of aminolevulinate synthase 2 (ALAS2), the first enzyme of heme biosynthesis (Figure 1).[2] In both, protoporphyrin released from erythroid cells into the vascular endothelium and surrounding tissues is activated by visible light, triggering oxidative stress and inflammation.[3] Patients are primarily sensitive to visible light in the blue range.[1] Both disorders present in childhood with severe, non-blistering phototoxicity preceded by characteristic prodromal symptoms, often including tingling, burning, or itching that serve as warning signals to avoid sun exposure.[1] Continued exposure leads to severe phototoxic pain that can be associated with erythema and swelling of sun-exposed skin, primarily the dorsum of the hands and face (Figures 2, S1). The pain is usually not responsive to analgesics, and recovery may take several days. Recurrent phototoxic episodes result in a conditioned behavior of sunlight avoidance and decreased quality of life.[4,5] In addition to phototoxic episodes, these disorders have multisystemic manifestations including hepatopathy, iron deficiency anemia, and vitamin D deficiency, which are often under-recognized.[1]

The mean diagnostic delay is over a decade, and evidence supports significant underdiagnosis.[6,7] The disease prevalence of EPP was estimated to be 1:109,000 in Europe, but more recent data using exome databases show a prevalence approximating 1:17,000 in Caucasians.[8,9]

There are few specialists with expertise in these rare disorders. Many patients are managed by dermatologists or primary care physicians with limited experience with these disorders and no standardization of care. Because new therapies are now available and more are in development, the diagnosis and identification of patients who may benefit from therapeutic interventions or need closer follow up for long-term complications is particularly important. Here, we provide the first evidence-based consensus guidelines for the diagnosis and management of these photodermatoses.

Scope

These guidelines address the diagnosis, monitoring, and management of patients with EPP and XLP (referred to collectively as protoporphyria in this manuscript) without evidence of liver disease. Management of protoporphyria-mediated hepatopathy and indications for liver or bone marrow transplantation are outside the scope of these guidelines. Multidisciplinary consultation at a center with hematology, hepatology, and liver transplantation expertise in protoporphyria is recommended for patients with progressive liver disease.

Methods

A systematic review of the literature was performed using best practices from the Cochrane Handbook for Systemic Reviews of Interventions and the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement.[10,11] The review examined all primary research studies pertaining to diagnosis and management using MESH headings “erythropoietic protoporphyria” and “X-linked protoporphyria,” including randomized

controlled trials, cohort studies, case-control studies, case reports, and cross-sectional studies. The search was conducted in the following databases with no language or date restrictions: PubMed, EMBASE, Web of Science, and Clinicaltrials.gov. Duplicates and conference abstracts were removed.

Inclusion criteria were studies related to the diagnosis and management of EPP or XLP and human or animal studies. Exclusion criteria were studies that were not accessible in English, did not pertain to EPP or XLP, conference abstracts, and non-primary research. Two reviewers independently screened titles and abstracts in Covidence using these pre-defined eligibility criteria, and differences in opinions were resolved by discussion and consultation with a third reviewer.[12] The full text of the remaining studies was screened for further exclusion (Figure S2).

A writing committee composed of 17 clinicians who were members of the Porphyrias Consortium and with recognized expertise were selected to establish diagnostic and management guidelines.[13] The committee included experts in dermatology, hematology, hepatology, genetics, neurology, and internal medicine, and one physician-patient. The committee was divided into the following topic subgroups: diagnosis, dermatology, hepatology, hematology, and miscellaneous. Members of each subgroup reviewed articles relevant to their topic. Subgroups arrived at evidence-based guidelines addressing the important diagnostic and management concerns for that topic. For diagnostic or management concerns with minimal to no evidence (level C evidence), recommendations were determined by consensus within each subgroup followed by the entire writing committee, achieved through a series of small and large group meetings and voting sessions. The word choices of the recommendations were selected to be consistent with the size of treatment effect, indicated by the recommendation class.[14]

Results

Diagnosis

Total erythrocyte protoporphyrin concentration, including proportions of metal-free and zinc-bound protoporphyrin, is the recommended test for the diagnosis of protoporphyria (Table 1).[15–17] The percentage of metal-free protoporphyrin is typically >90% in EPP and ~50–85% in XLP.[2] Minor elevations in protoporphyrin (mostly zinc-bound and/or <3x upper limit of normal) is not consistent with a diagnosis of protoporphyria, and further evaluation for other causes such as iron-deficiency anemia or lead intoxication can be beneficial.[15–17] Laboratories that can accurately fractionate metal-free and zinc-bound protoporphyrins are recommended to make the diagnosis (Table 1).[15–17] Clinicians should avoid laboratories that measure protoporphyrin only by hematofluorometry, which can lead to falsely normal levels of erythrocyte protoporphyrins, and these results are often incorrectly labeled as “free erythrocyte protoporphyrin.” Clinicians should refer to the United Porphyrias Association website for currently recommended laboratories.[18] Because exposure of samples to light may cause inaccuracies in protoporphyrin testing, instructions on light-protected specimen handling should be provided to both phlebotomists and patients.

In patients with protoporphyria, plasma porphyrin levels may be normal or increased. Elevated plasma porphyrins are not diagnostic of EPP and are therefore not recommended as first-line testing.[19] Urinary and fecal porphyrins are typically normal in protoporphyria, and testing is not recommended.[20,21] Skin biopsies are not indicated for the diagnosis of protoporphyria and should be reserved for cases where other diagnoses are being ruled out.[22]

If a diagnosis of protoporphyria is established based on significantly elevated protoporphyrin, genetic testing of the *FECH* and *ALAS2* genes is recommended to distinguish between EPP and XLP.[2] Approximately 4% of patients will not have a causative pathogenic variant identified even with elevated protoporphyrin.[1] The vast majority of patients with EPP are compound heterozygotes for both a rare pathogenic *FECH* variant and a common low expression *FECH* allele that is present in ~10% of the Caucasian population (c.315-48T>C), a combination that results in ~30% of normal enzyme activity.[2,8] Homozygosity for *FECH* c.315-48T>C does not cause EPP. [23] Genetic testing in the absence of biochemical testing is not recommended given the possibility of identifying variants of uncertain significance and the small percentage of patients in whom the genetic variant remains undefined. XLP accounts for 2–10% of protoporphyria cases and is caused by gain-of-function variants in exon 11 of *ALAS2* and follows an X-linked inheritance pattern.[24] Because of the possibility of skewed X-inactivation, disease severity in females can vary from mild to as severe as XLP males.[24] Genetic counseling is recommended for couples with a personal or family history of protoporphyria who are planning to have children.

Management of dermatologic symptoms

Pharmacologic management—Although various pharmacologic agents have been studied for EPP, only a few robust clinical studies evaluating efficacy are available.[25] Studies of afamelanotide, a subcutaneously administered, long-acting α-melanocyte stimulating hormone analogue demonstrate that it increases the duration of pain-free sun exposure and improves quality of life in adults with EPP.[25–29] Afamelanotide binds to the melanocortin-1 receptor (MC1R) and increases eumelanin production from dermal cells and melanocytes, thus increasing pigmentation and providing photoprotection. Melanin is additionally a strong antioxidant thought to inactivate the reactive oxygen species produced during phototoxic reactions.[30] Long term follow-up studies reported significant improvement in quality of life and a high rate of therapy continuation.[28] Therefore, afamelanotide is recommended for the prevention of phototoxic symptoms in EPP (Table 2).[25–29] For patients using afamelanotide, total body skin examinations by a dermatologist are recommended every 6 months. The drug is available in the US and Europe, however access is limited in the US due to the high cost and restricted sites for administration. There is no data on the safety of afamelanotide during pregnancy so this cannot be recommended for pregnant women. Due to insufficient data related to efficacy, the following therapies are not recommended for the prevention of phototoxic symptoms: beta-carotene, cysteine, cimetidine, isoniazid, warfarin, quinacrine, oral zinc, N-acetylcysteine, vitamin C, omega-3 fatty acids, oral adenosine monophosphate, canthaxanthine, terfenadine, inosine, dithiothreitol (DTT) and glycerol, pyridoxine, and hydroxyethylrutosides (Table 2).[25,31–52] Although several previous studies have investigated beta carotene in EPP, the evidence shows unclear or no benefit.[25,31,51,52] Dersimelagon

is a synthetic, orally administered, small molecule agonist of MC1R being tested for the prevention of protoporphyria phototoxicity. A positive Phase 2 clinical trial has been completed showing promising results, and a Phase 3 study is ongoing.[53] There are no approved therapies for pediatric patients.

Non-pharmacologic management—Sunlight avoidance and opaque clothing are recommended for the prevention of phototoxic symptoms in protoporphyria (Table 2).[5] Window tinting for cars can be useful. Because some patients report a small benefit with broad-spectrum and/or tinted sunscreens such as zinc oxide and titanium dioxide and because these agents block a portion of the far UVA wavelengths (350–399 nm) of light that activate protoporphyrin, it is reasonable for patients to use these agents for the prevention of phototoxic symptoms.[54] However, non-broad-spectrum or non-tinted sunscreens are not useful for prevention of phototoxic symptoms in protoporphyria.[55]

For patients without access to afamelanotide, limited natural sunlight exposure or low-dose hardening phototherapy with narrowband UVB increased slowly over time to induce a gradual increase in endogenous melanin production may be considered for prevention of phototoxic symptoms.[56,57]However the effectiveness of this therapy is unclear and not well established. For patients who are sensitive to indoor lighting, utilizing indoor lights that minimize the amount of blue light may be considered.

Depending on symptom severity, workplace/school accommodations and educating teachers about protoporphyria can be useful, as well as educating children regarding how to explain their disease and to advocate for themselves.[58] Protoporphyria patient groups (i.e., social media groups, patient advocacy group meetings, and disease-specific camps for families) can facilitate sharing advice and experiences and are recommended.[59]

Treatment of phototoxic symptoms—No studies evaluating treatments for acute phototoxicity could be found. Anecdotally, many patients choose to self-treat with ice, cold water, or cold compresses, resulting in minor relief, although others report that both cold and heat worsen symptoms. Cold compresses or cooling devices may be considered for the treatment of phototoxic symptoms (Table 2).[5,60] There is no evidence of benefit with narcotic analgesics, oral or topical corticosteroids, antihistamines, acetaminophen and non-steroidal anti-inflammatory drugs. There are insufficient data to recommend these therapies. The development of novel therapies to treat pain in protoporphyria patients is a large unmet need.

Safety of light/laser therapies—Laser therapies and other light-based therapies are considered safe if the wavelengths are outside the 350–650 nm range (Table 2). Spot treatment prior to full therapy is recommended regardless of the light wavelength used. For infants at risk for protoporphyria, therapy using bili lights is reasonable when required for treatment of hyperbilirubinemia, using conservative light doses and close monitoring for symptoms. To date, no reports exist of phototoxic symptoms in the perinatal period or with use of bili lights.

Management of anemia

A mild hypochromic, microcytic anemia is present in ~30–60% of patients with protoporphyria.[61–63] While phenotypically consistent with iron deficiency anemia, it remains unclear whether erythropoiesis is indeed iron restricted in EPP or whether the anemia reflects heme deficiency or another mechanism.[62–68]

Because of the risk of iron deficiency and anemia, it is reasonable for patients to have an annual CBC and iron panel (Table 1).[61–63] Iron supplementation may be considered for EPP patients who are symptomatic from iron deficiency and/or have hemoglobin levels <10 g/dL and ferritin <10 ug/L, with consideration of the individual's risk of worsened photosensitivity versus benefit from iron therapy, supplementing with oral iron to achieve a goal ferritin of 50–100 ug/L (Table 2).[61–68] Iron repletion is indicated for XLP patients with iron deficiency because the addition of iron in the context of normal FECH function is expected to improve erythrocyte protoporphyrin levels.[24,63,69,70]

Monitoring liver function

Elevations in liver transaminases can be seen in ~27% of EPP patients.[80] In ~2% of patients, this may progress to liver failure. Liver injury occurs from the crystallization of protoporphyrin in the bile ducts.[71] This obstruction of the biliary system further increases plasma protoporphyrin, which is typically excreted in the bile, escalating the protoporphyrin-mediated liver damage that may progress rapidly.[71] Previous studies indicate that higher protoporphyrin levels may be associated with an increased risk of liver disease or progression.[71] Genetic sequencing to identify EPP patients with two pathogenic *FECH* variants other than c.315-48T>C may be considered, as these patients may be more likely to progress to liver failure.[72] Liver chemistries should be performed at the time of diagnosis and at least yearly thereafter (Table 1).[73–75] This may allow for early identification, evaluation for additional factors contributing to liver disease, and medical management.

The extent to which alcohol use augments protoporphyria-related liver disease or whether a safe limit exists remains unclear. Avoidance of excessive alcohol intake is recommended for all patients. Furthermore, immunization against hepatitis A and B is recommended. Although protoporphyria patients are at an increased risk for cholelithiasis, in asymptomatic patients with normal liver chemistries, a screening ultrasound is not recommended. Cholecystectomy is not recommended for asymptomatic cholelithiasis.

Miscellaneous guidelines

Vitamin D deficiency management—There is an increased recognition of prevalence of vitamin D deficiency in protoporphyria patients due to lifelong sunlight avoidance. Routine screening for vitamin D deficiency and supplementation as per population guidelines are recommended (Table 1).[76,77]

Anxiety and Depression—Anxiety and depression due to disease-related symptoms have been reported. However, the rates of these conditions in adults are similar to the general population.[4,59,78] Patients should receive the same screening for anxiety/depression as the

general population.[4,59] The psychosocial impact of protoporphyria in children has not been well studied.

Pregnancy—Several reports describe improved protoporphyria symptoms in pregnancy, but these are inconsistent.[79–84] Patients do not have different perinatal outcomes from the general population.[84,85] Therefore, pregnant patients should receive the same routine medical and prenatal care with no need for increased monitoring for neonatal risks. No additional adjustments in light protection strategies are necessary during pregnancy.[5,84–87]

Surgical management—For protoporphyria patients undergoing endoscopy or non-prolonged duration surgery, no light modification is required.[88] In patients undergoing surgery of prolonged duration, such as liver transplantation, light filters that limit transmission of the wavelengths 340–470 nm (i.e., acrylate yellow filter) are recommended.[88,89] No specific anesthetic agents or other medications are contraindicated in protoporphyria.

Conclusion

EPP and XLP are multi-systemic disorders presenting with severe, acute phototoxicity leading to a conditioned behavior of sun avoidance, decreased quality of life, and, in rare cases, liver failure. Evidence-based diagnosis and management guidelines are essential to standardize care and to identify patients at risk for long-term complications, of particular relevance with the recent availability of novel therapeutics, and other drugs in development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Capsule summary

- This publication presents the first evidence-based consensus guidelines for the diagnosis and management of the phototoxic disorders erythropoietic protoporphyria and X-linked protoporphyria.
- These guidelines will allow dermatologists and other physicians to provide standardized care for the diagnosis and multisystem management of these patients.

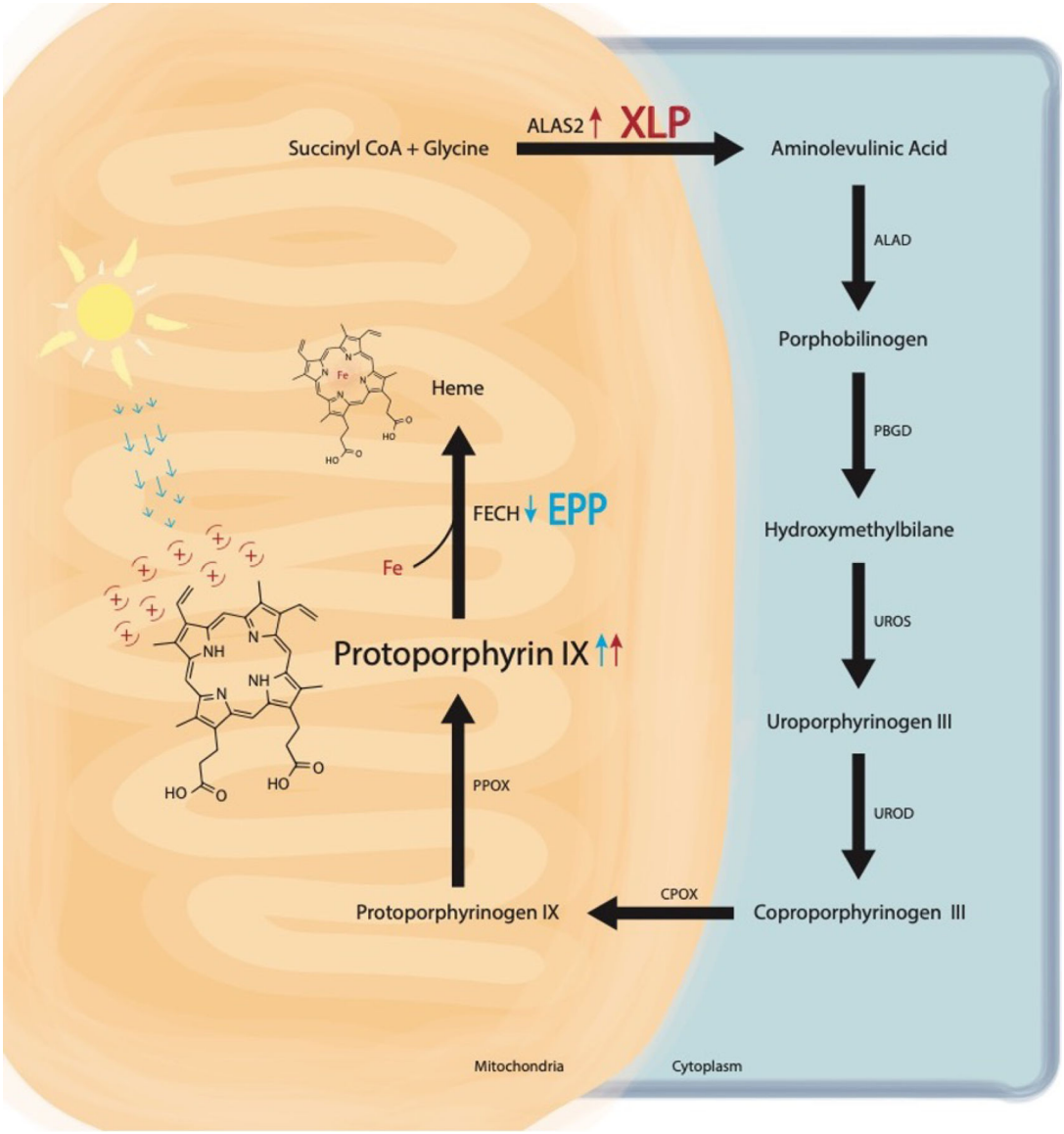

Figure 1. Molecular Pathophysiology of the Protoporphyrias

The heme biosynthetic pathway requires eight enzymatic steps. Gain-of-function variants in *ALAS2* result in X-linked protoporphyria (XLP), and loss-of-functions variants in *FECH* result in erythropoietic protoporphyria (EPP). In both, metal-free protoporphyrin IX accumulates in erythroblasts, erythrocytes, the plasma, and the biliary system. Metal-free protoporphyrin IX is photosensitive, particularly to visible light in the blue range, and the light-mediated activation of metal-free protoporphyrin IX produces free radicals that damage the surrounding tissues. ALAS2, aminolevulinate synthase 2; FECH, ferrochelatase; ALAD, delta-aminolevulinic acid dehydratase; PBGD, porphobilinogen dehydratase; UROS, uroporphyrinogen III synthase; UROD, uroporphyrinogen III decarboxylase; CPOX, coproporphyrinogen-III oxidase; PPOX, protoporphyrinogen oxidase

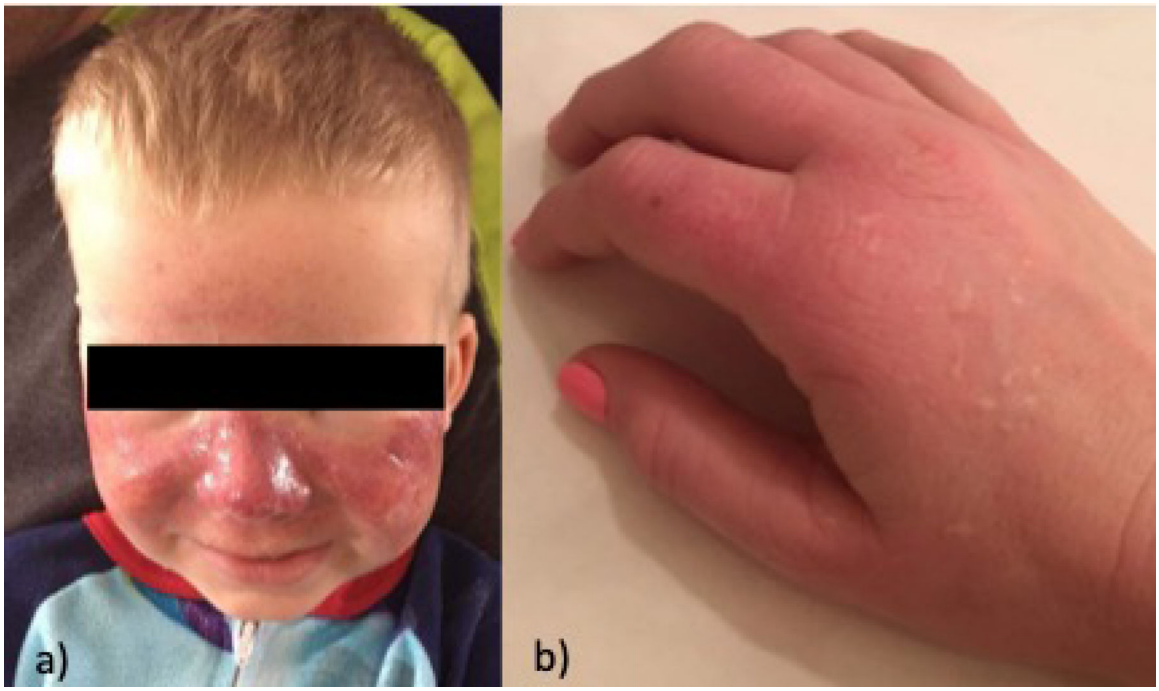

Figure 2.

Cutaneous findings in protoporphyria

a) Child with extensive edema of the face with erythema and petechiae

b) Adult patient with erythema and edema during phototoxic episode, with hypopigmented scars and skin thickening present

Of note, in protoporphyria, the skin may have no visible changes during severely painful phototoxic episodes.

Table 1

Diagnosis and Monitoring in Protoporphyria

Primary diagnostic test	**Laboratory tests that should be evaluated at least yearly**
• Total erythrocyte protoporphyrin with metal-free erythrocyte protoporphyrin fraction *Substantially elevated total erythrocyte protoporphyrin (>3x ULN) and majority metal-free is consistent with diagnosis.*	• Total erythrocyte protoporphyrin • Liver biochemistries, including Aspartate aminotransferase (AST), Alanine aminotransferase (AST), Total bilirubin, Alkaline phosphatase • Hemoglobin • Iron panel, including iron, total Iron Binding Capacity (TIBC), and ferritin • Vitamin D
Follow-up tests to distinguish EPP from XLP	**Monitoring for patients on afamelanotide**
• Molecular analysis of *FECH* and *ALAS2* *Pathogenic* FECH *variants seen in EPP and pathogenic C-terminal* ALAS2 *variants seen in XLP.* • Percent metal-free versus zinc-bound erythrocyte protoporphyrin *Metal-free erythrocyte protoporphyrin >90% in EPP and 50–85% in XLP*	• Whole body skin exam every 6 months
	Tests not recommended for diagnosis
	• Plasma porphyrins • Urinary porphyrins • Fecal porphyrins
	• Skin biopsy
Level of Evidence	
Class I, level B: benefit >>> risk, limited published data	
Class I, level C: benefit >>> risk, very limited to no published data	
Class III no benefit, level B: no benefit, limited published data	
Class III no benefit, level C: no benefit, very limited to no published data	

Table 2

Management of Protoporphyria

<table>
<tr><th>Medical and non-medical management for the prevention of phototoxic symptoms</th><th>Therapeutics with no clear benefit for the prevention of phototoxic symptoms</th></tr>
<tr><td>• Afamelanotide every 2 months
• Sunlight avoidance
• Opaque clothing
• Patient support groups
• For surgeries of prolonged duration, light filters that limit transmission of wavelengths 340–470 nm</td><td rowspan="4">• Beta carotene
• Cysteine
• Cimetidine
• Isoniazid
• Warfarin
• Quinacrine
• Oral zinc
• N-acetylcysteine
• Vitamin C
• Omega-3 fatty acids
• Oral adenosine monophosphate
• Canthaxanthine
• Terfenadine
• Inosine
• Dithiothreitol (DTT) and glycerol
• Pyridoxine
• Hydroxyethylrutosides</td></tr>
<tr><td>• Window tinting for cars
• Broad-spectrum and/or tintedsunscreens
• Workplace/school accommodations
• Educating teachers about EPP/XLP
• Educating children to explain their disease and advocate for their own light avoidance</td></tr>
<tr><td>• Use of indoor lights with minimal blue light

Management only to be considered in patients who are not a candidate for afamelanotide:
• Gradual increase in sunlight exposure over time
• UVB phototherapy</td></tr>
<tr><td>• Light modifications during endoscopy or non-prolonged duration laparoscopic or non-laparoscopic surgery</td></tr>
<tr><th>Management of phototoxic symptoms</th><th>Therapeutics with no clear benefit for the treatment of phototoxic symptoms</th></tr>
<tr><td>• Cold compresses
• Cooling devices</td><td rowspan="2">• Narcotic analgesics
• Oral or topical corticosteroids
• Antihistamines
• Acetaminophen
• NSAIDS</td></tr>
<tr><th>Iron deficiency in ferrochelatase-deficient EPP</th></tr>
<tr><td>If symptomatic from iron deficiency and/or have hemoglobin levels <10g/dL and ferritin <10ug/L:
• Iron supplementation to a goal ferritin of 50–100ug/L</td><td>Prevention of liver disease</td></tr>
<tr><th>Iron deficiency in XLP</th><td rowspan="2">• Avoidance of excessive alcohol intake
• Immunization against hepatitis A and B</td></tr>
<tr><td>If any iron deficiency:
• Oral iron to a goal ferritin of 50–100 ug/L</td></tr>
<tr><th>Pregnancy management</th><td rowspan="2">• Screening ultrasounds
• Cholecystectomy for asymptomatic cholelithiasis</td></tr>
<tr><td>• Routine medical and prenatal care</td></tr>
<tr><th colspan="2">Levels of Evidence</th></tr>
<tr><td colspan="2">Class I, level B: benefit >>> risk, limited published data</td></tr>
<tr><td colspan="2">Class I, level C: benefit >>> risk, very limited to no published data</td></tr>
</table>

Medical and non-medical management for the prevention of phototoxic symptoms	**Therapeutics with no clear benefit for the prevention of phototoxic symptoms**
Class IIa, level C: benefit >> risk, very limited to no published data	
Class IIb, level C: benefit > risk, very limited to no published data	
Class III no benefit, level B: no benefit, limited published data	
Class III no benefit, level C: no benefit, very limited to no published data	