Porphyrias – An Overview and Update for Physicians and their Staffs

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Abstract

Heme is an essential molecule involved in various biochemical processes in many species. It is used in the formation of cytochromes P-450, mitochondrial cytochromes, hemoproteins, catalase, peroxidase, myoglobin, and hemoglobin. Formation of the heme molecule involves a multistep process using eight enzymes. Biosynthesis of heme occurs in the mitochondria and in the cytoplasm. Most tissues in the human body synthesize heme, but the main sites of formation are in the bone marrow (erythroblasts) and in the liver (hepatocytes). Porphyrias are a unique group of disorders mainly due to inborn errors of metabolism of the heme synthetic pathway. The deficient activity of the enzymes can lead to a build-up of heme precursors, resulting in wide heterogeneity of clinical symptoms. To date, there are nine described porphyrias: aminolevulinic acid dehydratase deficient porphyria (ALADP), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), porphyria cutanea tarda (PCT), hepatoerythropoietic porphyria (HEP), congenital erythropoietic porphyria (CEP), erythropoietic protoporphyria (EPP), and X-linked protoporphyria (XLPP). The classification of porphyrias is based on 1) the main sites of heme precursor synthesis (hepatic, erythropoietic), 2) acute or chronic porphyria, and 3) cutaneous involvement. In this review, we focus on AIP, PCT, and EPP, the three most common forms of porphyria in the United States. A case vignette for each of the three is provided and followed by a discussion regarding the clinical features, pathogenesis, diagnosis/management, and prognosis of each. Management of AIP currently revolves around avoidance of drugs and chemicals and severe caloric deprivation, which may trigger acute attacks, and use of intravenous heme for acute attacks. Exciting new therapies, particularly siRNA to down regulate hepatic 5-aminolevulinic acid synthase, are under active development. Management of EPP currently involves protection from sunlight, but implants of afamelanotide have shown good efficacy and are already approved by the European Medicines Agency.

Abbreviations used: AFP – alpha-fetoprotein, AIP – acute intermittent porphyria, ALA – 5 [delta]-aminolevulinic acid, ALADP – aminolevulinic acid dehydratase deficient porphyria, ALAS-1 – 5-aminolevulinic acid synthase-1, CEP – congenital erythropoietic porphyria, CT – computed tomography, ePP – erythrocyte protoporphyrin, EPP – erythropoietic protoporphyria, GABA – gamma-amino butyric acid, HCC – Hepato-cellular carcinoma, HCP – hereditary coproporphyria, HCV – hepatitis C virus, HEP – hepatoerythropoietic porphyria, HFE – the gene mutated in the common, HLA-linked form of hereditary hemochromatosis, HIV – human immunodeficiency virus, PBG – porphobilinogen, PBGD – porphobilinogen deaminase, PCT – porphyria cutanea tarda, PP – protoporphyrin, UROD - uroporphyrinogen decarboxylase, VP – variegate porphyria, XLPP – X-linked protoporphyria

1. Introduction: Overview of the Porphyrias

Defects within the eight step process of heme synthesis result in the disabling effects of porphyria (Figure 1). The symptoms associated with the porphyrias are wide-ranging and often result in broad evaluations before a diagnosis is considered and confirmed. There are two broad categories of classification for the eight porphyrias: hepatic or erythropoietic and acute or chronic (Table 1). Porphyria is a disease that has been prevalent in both history books and folklore. It is believed that the first mention of porphyria was by Hippocrates in 460 BCE and some believe that King George III and Vincent van Gogh may have suffered from porphyria.[1-5] This review will focus on the three most common types of porphyria seen in the United States (US): acute intermittent porphyria (AIP), porphyria cutanea tarda (PCT), and erythropoietic protoporphyria (EPP).

Table 1. Main Schemes of Classification of the Porphyrias

	Acute Hepatic porphyrias	Chronic Hepatic porphyrias	Erythropoietic porphyrias
Types of porphyria	1. Aminolevulinic acid dehydratase deficient porphyria 2. Acute intermittent porphyria 3. Hereditary coproporphyria 4. Variegate porphyria	1. Porphyria cutanea tarda 2. Hepatoerythropoietic porphyria	1. Congenital erythropoietic porphyria 2. Erythropoietic protoporphyria 3. X-linked protoporphyria
Gender Frequency	Female > male [~4>1]	Male > female	
Site of origin	Liver	Liver	Bone marrow
Inheritance	Autosomal dominant – AIP, HCP, VP ALADP - autosomal recessive	Usually acquired. Autosomal recessive or co-dominant	Autosomal recessive – EPP X-linked-XLPP Autosomal recessive – CEP
Key clinical features	Neurovisceral symptoms Photocutaneous disease in HCP, VP	Cutaneous lesions on sun exposed areas, especially after minor mechanical trauma (painless blisters, skin fragility, sclerodermatous changes,. Cheeks and temples--hypertrichosis	CEP-- Cutaneous lesions on sun exposed areas (painless blisters, skin fragility, sclerodermatous changes, hypertrichosis) EPP, XLPP—Acute Burning, pain, pruritus, swelling after sun exposure
Key biochemical findings in active disease	ALADP—Increased urinary ALA, CP 3 AIP, HCP, VP—Increased urinary ALA, PBG, uroporphyrin 1, CP 3	Increased urinary Uro and heptacarboxyl- porphyrins, Increased stool isocoproporphyrins	CEP—increased urinary uroporphyrin 1, coproporphyrin 1, EPP, XLPP—Urine is normal unless hepatopathy has developed. Increased PP in plasma and RBCs

Abbreviations: AIP, Acute intermittent porphyria; ALA, 5-aminolevulinic acid; CEP, congenital erythropoietic porphyria; CP, coproporphyrin; EPP, erythropoietic protoporphyria; HCP, hereditary coproporphyria; PBG, porphobilinogen; VP, variegate porphyria.

Figure 1. Summary of the heme synthetic pathway, highlighting enzymatic defects associated with the porphyrias.

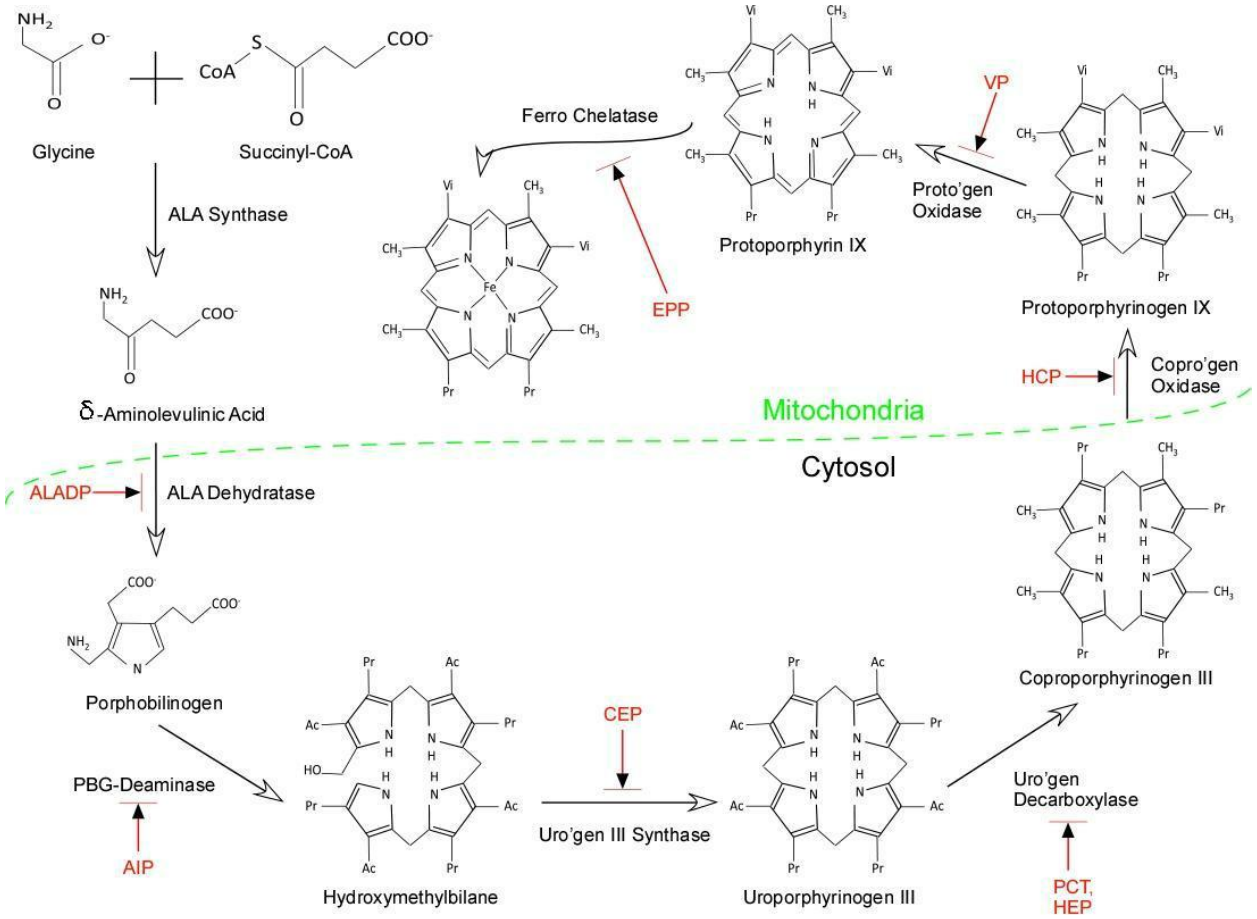

Figure 1. The heme synthetic pathway involves eight enzymes, four of which are active in the mitochondria, and four of which are active in the cytoplasm. The pathway is initiated and completed in the mitochondria. Intermediate steps in the cytoplasm begin with the activity of 5-aminolevulinic acid [ALA] dehydratase, also known as PBG synthase. Open arrows indicate progression through the pathway. Deficiency [indicated by blocked red arrows] in any of the eight enzymes involved in the pathway may contribute to development of acute or chronic hepatic porphyrias or erythropoietic porphyrias, as shown in red.

Abbreviations: Ac, acetate; AIP, acute intermittent porphyria; ALA, 5-aminolevulinic acid; ALADP, ALA dehydratase deficiency porphyria; CEP, congenital erythropoietic porphyria; copro'gen, coproporphyrinogen; EPP, erythropoietic protoporphyria; HCP, hereditary coproporphyria; HEP, hepatoreythropoietic porphyria; PBG, porphobilinogen; PCT, porphyria cutanea tarda; Pr, propionate; proto'gen, protoporphyrinogen; Uro'gen, uroporphyrinogen; Vi, vinyl; VP, variegate porphyria.

(Used with permission from Lane AM, McKay JT, Bonkovsky HL. Advances in the management of erythropoietic protoporphyria - role of afamelanotide. Appl Clin Genet. 2016; 9:179-189.)

2. The acute porphyrias – acute intermittent porphyria as the paradigm

2.1. Case Vignette

A 26-year-old woman, G0P0, with history of anxiety presented to the emergency room with severe, colicky lower abdominal pain that had been present in gradually ascending severity for the past 18 hours. Her abdominal pain, as before, was gradual in onset and did not improve with over the counter acetaminophen or naproxen. In addition to her abdominal pain, she also had noted fatigue, weakness, and difficulty with concentration for several days. She previously had presented twice to a local emergency room with similar symptoms over the past six months.

On review, she has been actively attempting to lose weight. She has been on a vigorous exercise and weight loss regimen over the past 5 months. She has not been prescribed any new medications. Currently, she is taking an oral contraceptive, which she has been taking for 3 years. She has a surgical history of an appendectomy 8 years ago. She has also been recently referred to her local general surgeon for consideration of a cholecystectomy because of her recurrent abdominal pain. She notes that, during episodes of recurrent pain, she develops nausea, anorexia, darkening of urine color and constipation.

In the emergency room, height was 67 inches; weight 175 lbs, BMI 27.4 kg/m^2; temperature was 98.6 F, blood pressure 152/84 mmHg, heart rate 107 beats/min, respiratory rate 18 breaths/min. She was oriented but lethargic and slow to respond to questions. The cardiopulmonary exam was normal. The abdomen was soft, nondistended, and nontender to palpation with hypoactive bowel sounds. A neurological exam revealed no focal deficits.

The laboratory evaluation revealed hyponatremia, with serum sodium = 128 mEq/L. Her remaining laboratory evaluation was normal including liver function tests, serum lipase and amylase, and a serum Helicobacter pylori antibody. In addition, a contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis was obtained and normal, as had three previous CT scans.

After receiving intravenous fluids and analgesics, she had improvement in her symptoms. Just prior to her discharge, she was witnessed by the emergency room staff to have a grand-mal seizure, and she was administered intravenous lorazepam.

She was admitted for additional observation. Given her young age, abdominal pain, hyponatremia, and seizure, a spot urinary porphobilinogen (PBG) and 5-[delta]-aminolevulinic acid (ALA) were checked and were found to be markedly elevated. Acute intermittent porphyria was suspected at this point. A 24-hour urine PBG was significantly elevated at 111 mg/d (reference range 0-4). She was administered intravenous hematin at 4 mg/kg/d for 4 days with improvement in her symptoms and was discharged in stable condition.

2.2. Clinical Features

The term “acute porphyria” was first coined by the Swedish internist Jan Waldenström to describe Swedish patients who had episodic neurologic crises.[6] The acute porphyrias can present with nonspecific symptoms. Patients who experience symptoms due to acute intermittent porphyria are often misdiagnosed and dismissed as having functional or psychosomatic pain. Some patients are also labeled as drug seekers given recurrent presentations for pain without a satisfactory response to analgesics.[7]

The acute hepatic porphyrias include aminolevulinic acid dehydratase deficient porphyria (ALADP), acute intermittent porphyria (AIP), hereditary coproporphyria

(HCP), and variegate porphyria (VP). The clinical characteristics of an acute porphyric attack are similar for each of the acute porphyrias, but are typically more severe in AIP.[8] It is thought that the buildup of heme precursors, especially of ALA, has effects on the nervous system, which causes most of the clinical symptoms. The acute attack, as in the foregoing clinical vignette, typically is characterized by severe abdominal pain, neurovisceral disturbances, and circulatory disturbances.[9]

Except for the very rare autosomal recessive ALADP form, it is atypical for persons with acute porphyrias to experience symptoms before the onset of puberty. Acute attacks are more common and severe in women than in men (ratio ~ 4:1). Acute attacks occur in women with peak incidence in the third and fourth decades of life.[9,10] It is less likely for women to experience acute attacks before menarche or after menopause. Medications, especially inducers of cytochromes P-450 and hepatic ALA synthase, and suicide substrates of cytochromes P-450, are major triggering or exacerbating factors. Others include progesterone and related chemicals, oral contraceptives, caloric deprivation, fasting, severe illness, and crash diets.[9,11,12]

Abdominal pain is regarded as a hallmark of an acute porphyric attack as it occurs in 85-90% of patients with AIP.[13,14] It is thought to be due to autonomic nervous system dysfunction. Patients can also have symptoms of nausea, vomiting, and constipation with abdominal imaging revealing a paralytic ileus.[9] Bowel sounds are often found to be decreased or absent on physical exam. Fever, diaphoresis, tachycardia, and systemic arterial hypertension, yet also with orthostatic hypotension, may also be present. These are evidence of sympathetic nervous system hyperactivity.

The acute porphyrias also exhibit effects on the central and peripheral nervous system. Peripheral neuropathy is a mostly motor neuron process due to axonal degeneration.[15] Patients who have frequent acute attacks can develop chronic neuropathic pain.[16] Patients can even develop respiratory failure and quadriparesis. When the central nervous system is involved, patients can present with irritability, insomnia, anxiety, paranoia, hallucinations, and psychoses.[9] Major motor seizures occur in up to 20% of acute porphyric attacks.[17] Treatment with anticonvulsants can be challenging as many of the commonly used anti-convulsants (barbiturates, hydantoins, valproate, etc) can precipitate and/or worsen acute porphyric attacks.

In addition to the psychiatric symptoms, schizophrenia and bipolar disorder have been associated with AIP. Waldenström observed that schizophrenia was common in families of patients with AIP.[31] In 1993, Sanders et al described an association between genetic variations of the porphobilinogen deaminase gene and schizophrenia.[32] Several studies after this have not been able to reproduce these findings however. Results from a Swedish study showed that individuals with AIP had a fourfold excess risk of being diagnosed with schizophrenia or bipolar disorder.[33] This study also showed an increased risk of schizophrenia and bipolar disorder in first degree relatives of individuals with AIP.

2.3. Pathogenesis

Porphyrias are caused by defects in genes of heme biosynthesis (Figure 1). These genetic disorders lead to high accumulations and toxic buildup of porphyrins and their precursors, ALA and PBG, which, respectively, can cause dermatologic and neurovisceral symptoms. These inborn errors of metabolism can lead to hepatic overproduction of the porphyrin precursors, ALA and PBG.

As already described, medications, fasting, and progesterone are among precipitating factors of the acute porphyrias.[18,19] There has been much interest regarding the pathogenesis of symptoms due to porphyria. Bonkovsky and Schady and others postulated two hypotheses regarding this: 1) cellular heme deficiency causing a significant reduction in heme-proteins in neuronal cells and 2) ALA being neurotoxic at the levels seen during an acute porphyria attack.[29] The causative factors are thought to increase the demand for hepatic heme. The decreased hepatic heme induces the synthesis of the housekeeping form of 5-aminolevulinic acid synthase (ALAS-1). This enzyme is known as the gateway for the biosynthesis of heme as it is not only the first enzyme in the pathway, but it is also normally the rate-limiting step in synthesis.

In AIP, the major metabolic defect is decreased activity (usually about 50% of normal) of hepatic PBG deaminase (PBGD), also known as hydroxymethyl bilane synthase. The inheritance is usually autosomal dominant, albeit with low clinical penetrance, due to several gene mutations.[9] PBGD is the third enzyme in the heme pathway, following ALA synthase and then ALA dehydratase (Figure 1). When precipitating factors are avoided, the reduced enzyme activity of PBGD adequately supplies hepatic heme to maintain normal functional status. When cytochrome P-450 enzymes are induced by certain medications or chemicals, the demand for heme is increased. This, in turn, leads to depression of hepatic ALAS-1 and to uncontrolled overproduction of ALA and, except for ALADP, also PBG. Additionally, it has been observed that certain medications/drugs can also directly activate ALAS-1. This ultimately results in a buildup of the heme precursors ALA and PBG due to the deficiency of PBGD.

ALA, PBG, and other hepatic heme precursors are thought to be able to cross the blood brain barrier.[9] Once this occurs, the heme precursors exert their neurotoxic effects throughout the brain. ALA is also structurally similar to gamma-amino butyric acid (GABA). Thus, it is believed that ALA has neurotoxic effects in the brain and also has the potential to bind to GABA receptors. Neurological symptoms such as mental status change and seizures are felt to be secondary to this mechanism. In all acute porphyrias, there are elevations in plasma and urine ALA levels, which reinforces the notion that it is a major pathogenic factor.

2.4. Management

See Table 2.

Table 2. Summary of Management of the Acute Porphyrias

	Recommendations
Dietary/Lifestyle modifications	- Avoidance of prolonged fasting states, crash diets - Avoidance of alcohol or minimal use - Diet balanced in carbohydrates (30-40 kcal/kg IBW/d) and protein (1-1.5 g/kg IBW/d) - Minimize excessive emotional stress, physical exertion - Identify precipitating agents and avoid known triggers
Laboratory evaluation	- Urinary ALA, PBG, porphyrins (markedly elevated during an acute attack) – spot urine sample [26] - Plasma and fecal porphyrins

	- Erythrocyte PBG deaminase level - Genetic testing/gene sequencing (if positive biochemical evaluation) - Monitor iron/ferritin levels - Electrolytes, renal/hepatic function
Acute porphyria attacks	- Goal is to reduce hepatic ALAS-1 activity - > 300 g carbohydrate per day (enterally or parenterally) - Intravenous hydration with 10% glucose solution daily - Analgesics: acetaminophen, meperidine, morphine - Intravenous heme 3-5 mg/kg daily for 3-5 days - Propranolol or nadolol (sympathetic hyperactivity) - Monitor urinary ALA, PBG
Hepatocellular carcinoma screening	- Age > 50 - Abdominal ultrasound (or alternative form of imaging) every 6-12 months - Serum AFP every 6-12 months
Special considerations - **Cyclical attacks associated with menstruation** - **Seizures**	- GnRH analogue, e.g., Leuprolide - Low dose oral contraceptives - Clonazepam, magnesium, gabapentin, levetiracetam have been shown to be tolerated
Frequent or refractory acute attacks	- Consider referral for liver transplantation
AFP – alpha-fetoprotein, ALA – 5- [delta]-aminolevulinic acid, g/kg – grams per kilogram, IBW/d – ideal body weight per day, mg/kg – milligrams per kilogram, PBG – porphobilinogen, ALAS-1 - 5-aminolevulinic acid synthase-1	

2.1. Prognosis

Acute porphyric attacks can last days to weeks. When managed adequately, symptoms typically improve in three to five days. During the interim between acute attacks, patients are mostly asymptomatic. Recurrent attacks can result in neuropathy and neurological deficits like wrist and foot drop.[16] However, motor symptoms are not always permanent and can resolve slowly over a period of months to years.

Studies of individuals with long-standing disease have revealed an increased prevalence of chronic kidney and liver disease.[20,21] The development of kidney disease has been found to be secondary to chronic tubulointerstitial nephropathy and focal cortical atrophy.[12,21] There have also been studies that suggest chronic kidney disease may be due to porphyria-associated nephropathy. This nephropathy is believed to be more likely to occur in patients who harbor a hypomorphic genetic variant in the human peptide transporter 2, which is a transporter of ALA.[22,23] The hypothesis is that more nephrotoxic ALA accumulates in those with the hypomorphic allele.

Patients with biochemically active acute hepatic porphyria are also at increased risk of developing hepatic fibrosis, which may progress to develop cirrhosis.[24] It is established that this cohort is at an increased risk of developing hepatocellular carcinoma

with a higher incidence between the ages of 50-60 years old.[25,26] Screening for hepatocellular carcinoma (HCC) with abdominal imaging and serum alpha-fetoprotein (AFP) levels are recommended in individuals age 50 or older, especially in those with frequent attacks or long standing biochemically active disease.

Novel therapies for acute porphyria are currently being developed. Gene therapy is one such alternative therapy. Currently, a method for delivering PBGD to hepatocytes via a viral vector is being studied. At this time, this approach has not shown significant improvement in ALA or PBG levels.[27] Investigation of the use of small interfering RNA (siRNA) directed against ALAS-1 is also underway. Givosiran (Alnylam Pharmaceuticals, Cambridge, MA) is a siRNA designed to target hepatic ALAS-1, which would lead to a reduction in ALA synthesis.[28] Preliminary studies have shown decreased expression of ALAS-1 after a single subcutaneous injection.[29] Individuals with severe, refractory, or recurrent attacks, despite optimal management, should be considered for orthotopic liver transplantation as this has been curative.[30]

The quality of life in any disease state is important to assess. A small study in Spain evaluated anthropometric and quality-of-life parameters in patients with AIP and showed statistically significant differences in certain anthropometric measures and in the quality of life assessed by the EuroQol-5D compared to controls.[35] These tools have the potential to be included in the armamentarium of clinicians to help guide care for patients with acute intermittent porphyria.

The greatest challenge currently still remains in making a diagnosis of acute hepatic porphyria in patients presenting with diverse features of acute attacks. Once established, prevention of future acute attacks is key and much effort continues at raising the awareness of diagnostic evaluation and management of the acute hepatic porphyrias.

3. Porphyria cutanea tarda

3.1. Case Vignette

A 57-year-old male with a family history including hemochromatosis and cirrhosis in his father presented for evaluation of blisters and vesicles on his hands. He had seen several local physicians who were unable to identify the etiology of his skin lesions. The patient reported smoking approximately 1/2 pack of cigarettes per day for approximately 20 years, and consuming up to a case of beer per day for approximately 15 years. He also formerly used intravenous drugs and intranasal cocaine. Physical exam was notable for scattered blisters, vesicles, and sores on the hands, and scalp. Some of the areas had a crusted appearance, but there were no signs of secondary infection. The liver edge was firm and palpable under the right costal margin. Complete blood count was within normal limits. Liver chemistries showed mildly elevated serum aminotransferase levels (AST 40, ALT 71) with normal total bilirubin and alkaline phosphatase. Serum ferritin was elevated at 516 ng/mL, and transferrin saturation was increased at 55%. A random spot urine revealed markedly increased urinary total porphyrins (2,250 mcg/g creatinine), with predominance of 8- and 7- [uro- and heptacarboxyl-] porphyrins. Plasma porphyrin was increased at 5 mcg/dL, also predominantly uro- and heptacarboxyl porphyrins, and the peak of fluorescence emission was at 620 nm. These findings established the diagnosis of PCT. Activity of uroporphyrinogen decarboxylase in erythrocytes was normal, and genetic testing of the uroporphyrinogen decarboxylase (*UROD*) gene revealed no mutations, indicating that the man had sporadic, acquired, type I PCT. Hepatitis C virus

(HCV) antibody was positive, and infection was confirmed with positive HCV RNA followed by HCV genotyping (1a). Genetic testing for hemochromatosis (*HFE*) was notable for compound heterozygosity for C282Y (major) and H63D (minor) mutations. Fibroscan showed median stiffness of 8 kPa corresponding to a Metavir fibrosis score of F2/4. Liver biopsy confirmed F2 disease, and showed moderate (2/4) iron staining, predominantly in periportal hepatocytes. The patient was strongly advised to discontinue alcohol consumption and tobacco use. Therapeutic phlebotomy was initiated weekly until serum ferritin had dropped to goal range (25-75 ng/mL), at which time HCV therapy with sofosbuvir/ledipasvir was initiated with regression of skin lesions and cure of HCV infection. PCT did not recur during 2 years of follow-up after these therapies.

3.2. Clinical Features

PCT, one of the chronic hepatic porphyrias is clinically characterized first and foremost by vesicles, bullae, blisters, and sores in sun exposed areas, most notably the hands. This does not represent acute photosensitivity, as is seen in EPP/X-linked protoporphyria (XLPP), but rather results from mild trauma to sun exposed areas, including forehead, ears, and neck. In contrast to acute porphyrias, there are no acute neurovisceral attacks, and the cutaneous manifestations are insidious in onset. With chronic and repeated trauma and ongoing sun exposure, chronic thickening of the skin with sclerodermatous-like changes may develop, as may small whitish papules, called 'milia.'

In most countries and regions, PCT is the most common type of porphyria in humans.[36] It is associated with iron loading in the liver and additional tissues. Iron overload is often related to a mutation in the hereditary hemochromatosis genes (typically *HFE*). Additional associations include excess alcohol use (alcohol-related liver disease), and cigarette use. Infections with chronic HCV or human immunodeficiency virus (HIV) are also associated with PCT. Hepatic involvement is characterized by elevated aminotransferase levels in conjunction with elevated iron indices.[37] Markers of hepatic synthetic function are generally normal at presentation.

3.3. Pathogenesis

The primary metabolic defect driving PCT is a deficiency in the activity of liver UROD. This enzyme's role is to convert uroporphyrinogen to coproporphyrinogen (Figure 1), which then goes on to form heme. Inhibition of this enzyme, whether through acquired deficiency of activity, or hereditary partial deficiency, in the presence of other risk factors, may result in accumulation of uro- and heptacarboxyl-porphyrins within hepatocytes. The major additional factors which diminish the activity of UROD include alcohol excess/alcohol-related liver disease, exposure to estrogens, chronic infection with HCV or HIV, and iron overload (usually related to *HFE* mutations).[38-45] A combination of these pathogenic factors is believed to induce oxidative stress within the liver leading to oxidation of uro- and heptacarboxyl-porphyrinogens to their corresponding porphyrins which are not substrates for UROD (Figure 2).

Figure 2. The molecular pathogenesis of porphyria cutanea tarda.

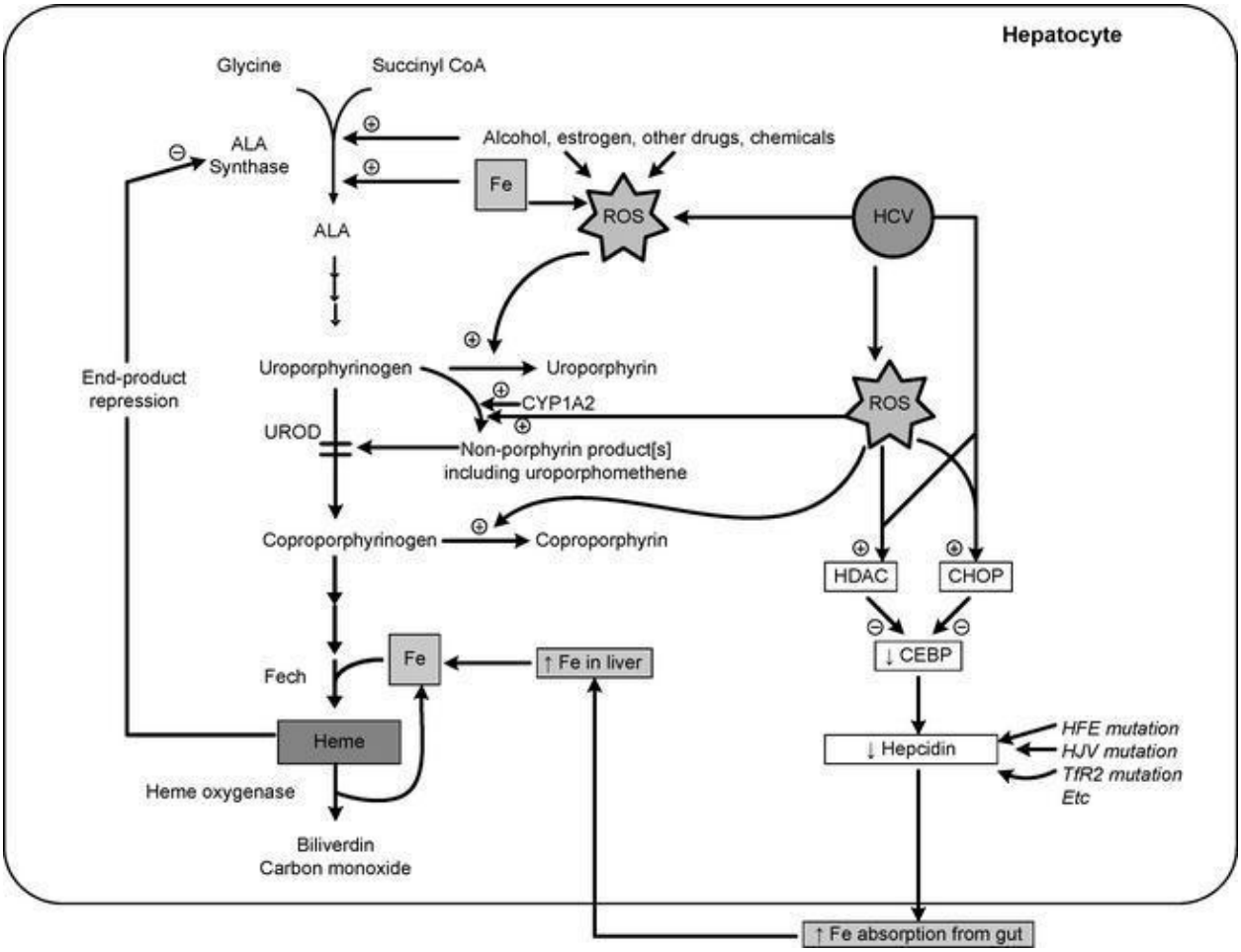

Figure 2. The central roles of increased reactive oxygen species, iron, and HCV infection are highlighted. (From Caballes FR et al. Liv Intl 2012; 32: 880-93, used with permission of the authors and publisher.)

3.4. Diagnosis and Management

Observation of the classic cutaneous manifestations as described above in conjunction with associated risk factors, should raise suspicion for PCT, and prompt further evaluation. The key diagnostic feature, is a marked increase in urinary porphyrins, with predominance of uro- and heptacarboxyl- porphyrins. A mild increase in urinary ALA and stool uroporphyrin and isocoproporphyrins can also be observed. Urinary PBG is normal.[46,47]

Treatment of PCT involves avoidance of sunlight and use of appropriate sunscreens and protection of sun-exposed skin to minor trauma. Additional interventions are aimed at modifiable risk factors, such as avoidance of alcohol, cigarettes, and estrogens. Treatment of underlying infectious precipitants such as HCV and HIV should be pursued.

In the presence of iron overload, therapeutic phlebotomy should commence with an initial goal of serum ferritin of 25 - 75 ng/mL. The use of low doses of antimalarial drugs (chloroquine or hydroxychloroquine, 100 mg initially twice or three times per week, with gradual increase to daily dosing over the first month) can be utilized to increase removal of porphyrins from hepatocytes (Table 3).[48] Remission of symptoms may take as long as six to nine months on therapy.

Table 3. Summary of Management of PCT

	Management/treatment	**Monitoring / Comments**
Behavioral	• Avoid sunlight • Utilize appropriate sunscreen / clothing • Alcohol and tobacco cessation	Most commercial sunscreen products of little or no value because they do not block long UV-blue light [Soret band]. Opaque zinc or titanium oxide pastes are effective. Protect especially the hands and forearms, face, neck
Dietary	-Avoid excess iron including: • Supplements • Red meats	
Iron removal	-Therapeutic phlebotomy • Weekly or Biweekly (~500 mL/session) • Avoid anemia (no phlebotomy if Hgb < 11 g/dL or Hct < 33%) -Chelation therapy • Deferasirox (10 mg/Kg/day) • Adverse effects: rash, hepatic/renal toxicity	Target ferritin (marker of total body iron) 25-75 ng/mL Particularly indicated in subjects with hemochromatosis. Volume of blood removed may be modified if necessary—for example small subjects may have only ~300 mL blood removed/ session. Chelation therapy more expensive and with more frequent adverse effects, but may be indicated in those with anemia, such as in setting of ESRD.
Antimalarials * As an adjunct to iron removal	-Chloroquine (125 mg twice/week) • Can be used as monotherapy if anemic -Hydroxychloroquine (200 mg twice/week)	Risk of relapse likely higher than after iron reduction therapy
Antiviral	-Hepatitis C therapy • Genotype - dependent • Current DAA regimens are well-tolerated	HCV RNA levels Follow recommended guidelines of AASLD/IDSA
AASLD, American Association for the Study of Liver Diseases; DAA, direct acting antivirals; ESRD, end-stage renal disease; HCV, hepatitis C; Hgb, hemoglobin; Hct, hematocrit; IDSA, Infectious Disease Society of America.		

3.5. Prognosis

Although the long-term prognosis is generally favorable for patients with PCT who are treated, the severity of underlying liver ultimately drives prognosis. The prevalence of HCV and or alcohol-related liver injury in conjunction with the hepatic injury from PCT may result in advanced fibrosis or cirrhosis in these patients. Generally, liver transplant may be needed in these patients secondary to alcohol or HCV-related liver disease. These patients are at increased risk for HCC, and should be screened with abdominal ultrasound and AFP every six months. Screening for varices should be pursued as clinically appropriate.

3.6. Hepatoerythropoietic Porphyria (HEP)---Severe Homozygous/Compound Heterozygous Form of PCT

HEP is an uncommon inherited cutaneous porphyria which results from severe deficiency of UROD, usually due to compound heterozygous defects, or, rarely, a homozygous defect.[49,50] Notably, the enzyme defect occurs in all cells and tissues. This condition is rare, and typically presents in infancy with severe photosensitivity with the formation of blisters and vesicles, closely resembling the cutaneous findings of congenital erythropoietic porphyria (CEP) in children or PCT in adults. Management is difficult and yields less definitive results compared to other porphyrias. Avoidance of sunlight, protection of the skin, and prompt management of infectious complications is paramount. Data supporting the use of iron removal and antimalarial drugs have been disappointing.

Liver transplantation can be utilized for treatment, as the overproduction of porphyrins occurs predominately in the liver. However, because the defect is present in all cells, overproduction of porphyrins may persist after liver transplant, and bone marrow transplant may also be needed for definitive management.[51]

4. Erythropoietic Protoporphyria and X-linked Protoporphyria

4.1. Case Vignette

A 21-year-old Caucasian man presented with a rash and abnormalities on screening tests from a community health fair. The patient stated he had had a "sun allergy" his "entire life" with development of burning, tingling, and pain after even very short periods of exposure (~15 minutes). He had seen multiple pediatric specialists without a definitive diagnosis. He endorsed a history of depressed affect as a result of avoiding sunlight and had undergone a cholecystectomy at age 20 (also had undergone liver biopsy during that operation), but otherwise stated he had been well. He was afebrile with unremarkable vital signs and brought recent lab results that showed a cholestatic liver injury with serum alkaline phosphatase 220 IU/L, total bilirubin 2.2 mg/dL, AST 49 IU/L, and ALT 51 IU/L. He also had a mild hypochromic, microcytic anemia with blood hemoglobin 10.8 g/dL and an MCV of 77 FL and hypovitaminosis D with a level of 19 ng/mL (ref range 30-100). Upon review of his prior evaluation, his liver biopsy showed crystal depositions which were birefringent on polarized microscopy with a Maltese cross pattern, sparse biliary canaliculi plugging with brown pigment, as well as early bridging fibrosis; his gallbladder contained pigmented stones. He had undergone urinary porphyrin studies, which were normal, shortly after his cholecystectomy. Physical examination revealed pale skin with hyperkeratotic patches on his knuckles, nose, and perioral area, but was otherwise normal. Labs from his current visit showed markedly elevated erythrocyte protoporphyrin levels (2150 mcg/dL, ref range 20-80), with 5% being zinc protoporphyrin and 95% metal-free protoporphyrin. Plasma porphyrin was also increased, 18 mcg/dL (ref range 0-1.0), and with fluorescence emission peak at 634 nm, following excitation by the Soret band

of blue light (410 nm peak for excitation). Based upon these results, as well as the history and physical examination, a diagnosis of classical EPP was made. Gene mutation analysis of the *FECH* gene revealed a nonsense mutation on one allele (p C411X) and the low-expressing common alteration on the other allele (IVS3-48 T>C), confirming classical erythropoietic protoporphyria due to deficient activity of FECH.

4.2. Clinical Features

The prodrome and subsequent dermatologic changes associated with EPP present a unique challenge in diagnosis, as the phenotype varies widely and may mimic more common presentations such as contact dermatitis, solar urticaria, drug eruptions, and other cutaneous porphyrias.[9]

Stereotypical presentation of EPP involves a painful reaction to even brief exposure to sunlight. The average age of onset is four years-old based on data from the largest cohort available, and symptoms can begin after fewer than ten minutes of sun exposure – the majority of patients have symptoms within 30 minutes.[52] The duration to onset of symptoms has been shown to be directly related to the levels of erythrocyte protoporphyrin (ePP), with higher levels portending a lower tolerance to light exposure.[52] Typically patients develop "burning" (91%), "tingling" (78%), and "itching" (78%) with light exposure which, with continuing light exposure, progresses to erythematous, edematous, and occasionally petechial lesions on the exposed skin that may last for hours to days and are typically refractory to even high-potency analgesia.[52] Of importance, and in notable contrast to other forms of cutaneous porphyria, such as PCT, HEP, CEP, or VP, vesicles and blisters are distinctly uncommon and only occur with extended exposure to sunlight.[9] As EPP is a chronic cutaneous porphyria, hyperkeratosis and lichenification may develop, as was noted with the patient in the above clinical vignette, and these lesions principally affect the knuckles and face in either a malar or perioral distribution.[9,52]

There are common coexisting clinical findings in patients afflicted with EPP such as iron deficiency anemia, hypovitaminosis D, decreased quality of life, pigment gallstones, and liver dysfunction varying from mild elevations in liver enzymes to fulminant hepatic failure.[53-55] Iron deficiency anemia is seen in approximately half of patients with EPP, and some circumstantial evidence suggests that symptoms may improve with iron repletion, although the opposite effect also has been described.[52, 56-59] Gallstones are seen in approximately a quarter of patients, and EPP should be suspected in all patients with pigment gallstones, especially in those without evidence of hemolysis. Decreased quality of life and vitamin D deficiency stem from the necessity of avoiding sunlight. Liver disease, as will be discussed in detail, varies in its severity, though typically presents as a cholestatic liver injury due to intracellular and canalicular crystal deposition. Of note, liver disease, as with other clinical manifestations of EPP, becomes more prevalent with higher ePP levels.[52]

4.3. Pathogenesis

Classical EPP stems from a genetic defect which affects the inner mitochondrial enzyme, ferrochelatase (or FECH).[60] When deficient, as in EPP, FECH is reduced in its ability to convert protoporphyrin (PP) into heme.[9] The final step in heme biosynthesis, namely insertion of Fe^{+2} into PP, performed by ferrochelatase converts the fluorescent PP molecule into non-fluorescent heme (Figure 1).[9] In patients afflicted with EPP, FECH activity is markedly reduced to approximately 10-30% of normal controls; thus the end-product of decreased FECH

activity is accumulation of PP.[9,54] PP is a strongly lipophilic molecule which allows for it to pass from erythrocytes to plasma and subcutaneous tissues.[62] As opposed to porphyria cutanea tarda and congenital erythropoietic porphyria where reactive species are in circulation, in EPP, PP is deposited into the skin because of the lipophilic properties.[52] The aforementioned fluorescent properties of PP become clinically evident after exposure to light, specifically blue light within the Soret band region (380-420nm), which results in excitation of the PP molecule into a high energy triplet state.[62] As these higher energy molecules return to lower energy states, they give rise to oxygen-containing free radicals that damage the tissues and vasculature where PP has deposited. It should be noted that blue light passes through windows and is produced by high-intensity light bulbs, namely, those used in medical and dental procedures. Because PP is strongly lipophilic, any circulating PP is cleared from the circulation only by uptake into hepatocytes and subsequent secretion into the bile. Thus, the urine is clear of PP and testing for urinary porphyrins is ineffective for diagnosis of EPP or XLPP.

Genetic mechanisms of EPP have been elucidated and originate from mutations of the *FECH* gene, which is located on chromosome 18q21.3.[61] A majority of EPP cases are the result of a *FECH* mutation [missense, nonsense, frame shift, or deletion] on one allele in *trans* with the common hypomorphic variation in intron 3 (IVS3-48 T>C) on the other allele, as in the case presented above. Much less common, but still important entities within the genetic underpinnings of EPP are a *FECH* mutation on both alleles and an acquired form of the *FECH* mutation, typically from a myeloid disorder.

More recent data have unveiled a closely related phenotype with similar accumulation of PP, namely, XLPP, in which the *FECH* gene is unaffected but rather in which there is a gain-in-function mutation (usually a deletion near the C-terminal) of the 5-aminolevulinate synthase-2 (*ALAS2*) gene, which is located on the X chromosome, hence the name X-linked PP.[7,63] About 5-10% of patients with the protoporphyric phenotype have XLPP.[64-66] The levels of zinc PP in erythrocytes are decidedly higher in XLPP, helping distinguish the two entities on diagnostic testing. Subjects with XLPP tend to have higher levels of ePP, more severe clinical disease, and higher risks of development of PP hepatopathy.

4.4. Diagnosis and Management

Diagnosis of EPP/XLPP requires documentation of elevated ePP levels. The screening test is total blood porphyrin with reflex testing of metal-free PP and zinc PP. If total blood porphyrins are elevated, and metal-free PP is >90%, then sequencing of the *FECH* gene will usually confirm EPP. If total blood porphyrins are elevated but the metal-free PP is 50-85% (with the remainder being zinc PP), exon 11 of the *ALAS2* gene should be sequenced as this likely represents XLPP. Most of the gain-of-function mutations in *ALAS2* are deletions of exon 11, which is a mutational 'hotspot.'

The mainstay of an effective EPP treatment regimen, at this juncture, is avoidance of blue light. Importantly, transparent sunscreens block only ultraviolet light and are ineffective in protecting EPP patients from the damaging effects of blue light.[9] Occasionally, and typically in those with darker complexions, light tanning can help extend the symptom-free interval with exposure to sunlight.[67] Because of the prevalence of gallstones and liver injury due to crystallization of the PP during its excretion in bile, surveillance for gallstones is warranted on an annual basis and liver function testing is warranted on a semi-annual basis.[68] Of note, rising ePP levels

may be a harbinger of liver disease and should be monitored more closely, concomitantly with liver function tests.[52] Given the risk of liver dysfunction due to high PP levels, hepatotoxins should be avoided and vaccination against viral hepatitis A and B should also be performed. Anything that causes cholestasis is likely to make EPP/XLPP markedly worse. The commonality of anemia and hypovitaminosis D implies that patients should be screened for these issues and iron and vitamin D supplementation provided as necessary. Various other modalities of treatment have been suggested, though convincing data for their use are limited. These include high dose cimetidine, activated charcoal, colestipol, beta-carotene, plasmapheresis, red blood cell exchange transfusion, and intravenous heme.[68-74] Table 4 provides a summary of principles of management of EPP and XLPP.

Table 4. Summary of Management of EPP and XLPP

	Management/treatment	Monitoring / Comments
Behavioral	• Avoid sunlight • Utilize appropriate sunscreen / clothing • Alcohol and tobacco cessation • Light tanning	Most commercial sunscreen products of little or no value because they do not block long UV-blue light (Soret band). Opaque zinc or titanium oxide pastes are effective. Tanning is generally recommended in those with darker complexions.
Laboratory and diagnostics	• Annual or semi-annual liver function testing • Annual surveillance for gallstones	ePP levels should be monitored concomitantly with liver testing.
Vaccination and supplements	• Ensure vaccination against hepatitis A and B • Replete vitamin D and iron as necessary	Iron deficiency and vitamin D are common but routine screening intervals have not been well defined.
Medications	• Afamelanotide 16mg subcutaneous injection every 60 days	Afamelanotide is pending US FDA approval. Numerous additional therapies have been proposed with minimal or conflicting evidence.
ePP, erythrocytic protoporphyria; mg, milligram; US FDA, United States Food and Drug Administration.		

Progressive liver dysfunction may ultimately necessitate orthotopic liver transplantation; however, the underlying physiology of liver dysfunction remains and thus, bone marrow transplantation (which, if successful, is curative) is occasionally considered for this reason.[75,76]

The severity of EPP/XLPP is generally less in patients with greater natural skin pigmentation, such as in African-Americans, compared to fair-complexioned Caucasians. Patients with greater innate skin pigmentation may be able to gradually increase their endogenous eumelanin by

graded doses of sunlight in the spring. Drugs that stimulate eumelanin production show promise as therapy. One such drug, afamelanotide, has been approved for restricted use in Europe by the EMA. Pending United States Food and Drug Administration approval, afamelanotide may become an option for EPP/XLPP patients also in the United States, as it has been shown to reliably increase the symptom-free time during light exposure and improve quality of life.[77-79] Afamelanotide is a congener of α-melanocyte-stimulating hormone, which works to increase production of eumelanin.[67] Afamelanotide increases eumelanin without the need for sunlight exposure; this well-tolerated therapy helps block the harmful effects of blue light while also reducing cytokine production, which helps reduce inflammation. [67,78,79]

4.5. Prognosis

EPP/XLPP is a chronic disease, and, if managed appropriately, serious complications can usually be avoided. Still, significant limitations in quality of life remain for affected individuals. Severity of disease has been shown to relate to higher ePP levels as well as lighter complexions.[51] The most serious consequence of EPP/XLPP lies in the hepatic dysfunction that occurs in approximately 5% of cases, and unfortunately, progresses to end-stage liver disease in 3-5% of patients.[9] Of note, higher levels of ePP and plasma PP levels increase the risk of PP hepatopathy. Such higher levels occur especially in XLPP (particularly males) to as does missense or nonsense mutations of both alleles of the *FECH* gene.[51] Genetic testing is recommended to verify the diagnosis as well as to help guide counseling for family members.

5. Summary and Conclusions

The porphyrias are a group of eight diseases, due mainly to inherited defects in genes and enzymes of normal heme biosynthesis. They present clinically in three different ways, as summarized above in the clinical vignettes presented: 1. Acute porphyrias--As acute attacks of severe pain, usually abdominal, in women aged 18-45 years, often with tachycardia, systemic arterial hypertension, and passage of dark reddish to purple colored urine, which may become even darker after exposure to light and air, especially at warm room temperatures; 2. Porphyria cutanea tarda--As skin lesions especially on the backs of the hands and forearms, and sometimes also the neck, ears, and head (areas of chronic sun exposure), occurring mainly in middle-aged men who drink alcohol, have iron overload, and/or HCV infection; and 3. EPP/XLPP--As acute almost immediate photosensitivity, with itching, burning, and pain of skin following minutes of exposure to sunlight. Clinicians need to keep these diagnoses in mind and especially need to order the correct key tests to establish or to exclude the diagnosis of a porphyria. There are new treatments that are under study for these disorders, especially Givosiran for acute porphyrias and direct-acting antiviral drugs for PCT in the setting of HCV infection. There also is evidence that some patients with EPP/XLPP may respond favorably to iron replacement therapy. At our medical center and others of the Porphyrias Consortium of the USA, we are actively studying these newer treatments in organized clinical trials, and we welcome inquiries from physicians and other providers who may have subjects eligible for these studies. Please contact Dee Faust (delannin@wakehealth.edu; phone: 336-713-1441) or Herbert L. Bonkovsky, (hbonkovs@wakehealth.edu) for more information or to refer patients for these studies. Continuing research is the key to improving care for these patients.

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