Recommendations for the Diagnosis and Treatment of the Acute Porphyrias

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The acute porphyrias, 4 inherited disorders of heme biosynthesis, cause life-threatening attacks of neurovisceral symptoms that mimic many other acute medical and psychiatric conditions. Lack of clinical recognition often delays effective treatment, and inappropriate diagnostic tests may lead to misdiagnosis and inappropriate treatment. We review the clinical manifestations, pathophysiology, and genetics of the acute porphyrias and provide recommendations for diagnosis and treatment on the basis of reviews of the literature and clinical experience.

An acute porphyria should be considered in many patients with unexplained abdominal pain or other characteristic symptoms. The diagnosis can be rapidly confirmed by demonstration of a markedly increased urinary porphobilinogen level by using a single-void urine specimen. This specimen should also be saved for quantitative measurement of porphobilinogen, 5-aminolevulinic acid, and total porphyrin levels. Intravenous hemin therapy, started as soon as possible, is the most effective treatment. Intravenous glucose alone is appropriate only for mild attacks (mild pain, no paresis or hyponatremia) or until hemin is available. Precipitating factors should be eliminated, and appropriate supportive and symptomatic therapy should be initiated. Prompt diagnosis and treatment greatly improve prognosis and may prevent development of severe or chronic neuropathic symptoms. We recommend identification of at-risk relatives through enzymatic or gene studies.

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The acute porphyrias are well-defined genetic disorders of heme biosynthesis characterized by acute life-threatening attacks of nonspecific neurologic symptoms (1). Although the specific enzyme and gene defects have been identified, diagnosis and treatment of these 4 disorders still present formidable challenges because their symptoms and signs mimic other, more common conditions. Delaying diagnosis and treatment of acute porphyric attacks can be fatal or can cause long-term or permanent neurologic damage. Updated, consistent recommendations for timely diagnosis and treatment of these disorders have been lacking, despite the existence of rapid, sensitive, and specific biochemical tests (2) and the availability of an effective therapy, which was first described more than 30 years ago (3) and was approved by the U.S. Food and Drug Administration (FDA) more than 20 years ago.

Formation of an Expert Panel and Basis of Recommendations

Concerns about misdiagnosis, delayed diagnosis, and inappropriate therapy prompted the American Porphyria Foundation to assemble a panel of experts on the acute porphyrias who were selected on the basis of their clinical and research experience and their contributions to the medical literature. The panel, which represents specialties including internal medicine, pediatrics, genetics, gastroenterology, hepatology, and hematology, was charged with formulating updated recommendations for diagnosing and treating the acute porphyrias.

With support from the American Porphyria Foundation, the panel members convened for a day-long meeting to formulate clinical recommendations. Two members, assisted by a medical writer funded by the Foundation, prepared a draft manuscript based on the panel's discussion and recommendations. All panel members participated in the review and revision of the manuscript and agreed to the final version.

Recommendations are based on the clinical experience of the authors and their review of the literature. Because the acute porphyrias are rare, most of the literature consists of reviews, small series, and case studies. A detailed MEDLINE search on treatment of acute attacks, for example, revealed 71 papers (55 in English and 16 with English abstracts) published between 1966 and October 2004. Of these, 41 were single-case reports, 13 were case series of 10 or fewer patients, and 17 (11 in English) were studies with more than 10 patients (4–20). Altogether, 53 papers discuss more than 1000 patients who received hemin therapy with or without initial treatment with glucose.

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Early Diagnosis of Acute Porphyria

Consider in all adults with unexplained symptoms seen in acute porphyrias (**Table 2**); certain clinical features are suggestive: women of reproductive age; abdominal pain; muscle weakness; hyponatremia; and dark or reddish urine.

Establish diagnosis promptly by testing for increased porphobilinogen in a single-void urine (we recommend the Trace PBG Kit [Thermo Trace/DMA, Arlington, Texas]).

If porphobilinogen is increased, begin treatment immediately. To establish the type of acute porphyria, save the same urine sample for measurement of ALA, porphobilinogen, and porphyrin levels, and measure plasma porphyrin levels, fecal porphyrin levels, and erythrocyte porphobilinogen deaminase levels (**Table 5** and **Figure**).

Treatment of the Acute Attack

Hospitalize patient for control of acute symptoms and withdraw all unsafe medications (see **Table 3**) and other possible precipitating factors.

Provide nutritional support and symptomatic and supportive treatment; consider seizure precautions, especially if patient is hyponatremic; use medications that are known to be safe in the acute porphyrias; and use intravenous fluids to correct dehydration and electrolyte imbalances, narcotic analgesics for pain, phenothiazine for nausea or vomiting, and β-adrenergic blockers for hypertension and symptomatic tachycardia.

Begin hemin (3 to 4 mg daily for at least 4 days) as soon as possible. Intravenous glucose alone (10%, at least 300 g daily) may resolve mild attacks (mild pain, no paresis, or hyponatremia) or can be given while awaiting delivery of hemin.

Monitor patient closely: Check vital capacity (if impaired, place patient in intensive care) and neurologic status, including muscle strength (especially proximal); check serum electrolytes, creatinine, and magnesium levels at least daily; and watch for bladder distention.

Follow-up

Educate patient and family about the disease, its inheritance, precipitating factors, and important preventive measures.

Encourage patients to wear medical alert bracelets and keep records of diagnostic studies and recommended therapy.

Treat chronic manifestations (such as pain and depression) and disability. Provide access to genetic testing for patient and family members.

role in the literature review, the formulation of recommendations, or the drafting and revising of the manuscript.

Overview of the Acute Porphyrias

Acute Porphyrias Are Inborn Errors of Heme Biosynthesis

Each of the acute porphyrias results from the deficient activity of a distinct enzyme in the heme biosynthetic pathway (1). Porphyrias are classified as hepatic or erythroid, depending on whether most of the heme biosynthetic intermediates arise from, and accumulate in, the liver or in developing erythrocytes. They are also classified clinically as acute or cutaneous on the basis of their major clinical manifestations. Of the 5 hepatic porphyrias, 4 characteristically present with acute attacks of neurologic manifestations—hence the designation *acute porphyrias*, a term that does not fully describe the clinical features, which can be prolonged and chronic.

Table 1 shows the genetic and enzymatic features of the 4 acute hepatic porphyrias (21): acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, and the very rare 5-aminolevulinic acid (ALA)–dehydratase porphyria. The combined prevalence of these diseases is approximately 5 cases per 100 000 persons (1). Numerous mutations have been identified for each disorder. The major manifestations of the acute porphyrias are neurologic, including neuropathic abdominal pain, peripheral neuropathy, and mental disturbances (**Table 2**) (1, 4, 22–25). These develop during adult life, are more common in women than in men, and are treated by methods to restore heme homeostasis. Variegate porphyria and, much less commonly, hereditary coproporphyria can also cause chronic, blistering lesions on sun-exposed skin that are identical to those in porphyria cutanea tarda, a much more common condition. Photocutaneous lesions may occur without neuropathic manifestations.

In addition to their highly variable neurologic signs and symptoms, the acute porphyrias are distinct from other porphyrias because of their common overproduction of the porphyrin precursors ALA (an amino acid), and porphobilinogen (a pyrrole). This striking biochemical feature is important for laboratory diagnosis and has implications for pathogenesis of the neurologic manifestations. While porphyrins (tetrapyrroles) are also increased, their measurement is of little value for initial diagnosis because they are also increased (in urine, feces, erythrocytes, or plasma) in other porphyrias and many other medical conditions.

Pathogenesis of Acute Attacks

The enzyme deficiency in each disorder is partial (approximately 50% of normal in the 3 most common acute porphyrias), and the remaining enzyme activity is usually sufficient for heme homeostasis. Because ALA dehydratase activity normally greatly exceeds that of the other enzymes in the pathway, a more severe deficiency of this enzyme ($\leq$5% of normal) is required to cause manifestations of ALA-dehydratase porphyria. These enzymatic defects "predispose" the affected persons to the effects of precipitating factors, including many drugs (for example, barbiturates, anticonvulsants, rifampin, and progestins), endogenous steroid hormones (especially progesterone), fasting, dieting, smoking, and stress from illness, all of which can increase the demand for hepatic heme and induce synthesis of ALA synthase, the first enzyme in the heme biosynthetic pathway. Because hepatic ALA synthase is rate-controlling, production of heme pathway intermediates increases to the

Table 1. **Characteristics of the 4 Acute Porphyrias***

Disease (Abbreviation)	Inheritance	Deficient Enzymes (Synonyms; Sequence in Pathway)	Subcellular Locations	Enzyme Activity, % *of normal*	Known Mutations, *n*†	Gene Locus	OMIM Number‡
Acute intermittent porphyria (AIP)	Autosomal dominant	PBG deaminase (HMB synthase; third)§	Cytosolic	~50	227	11q23.3	+176000
Hereditary coproporphyria (HCP)	Autosomal dominant	Coproporphyrinogen oxidase (sixth)	Mitochondrial	~50	36	3q12	+121300
Variegate porphyria (VP)	Autosomal dominant	Protoporphyrinogen oxidase (seventh)	Mitochondrial	~50	120	1q22	#176200
ALA-dehydratase deficient porphyria (ADP)	Autosomal recessive	ALA dehydratase (porphobilinogen synthase; second)	Cytosolic	~5	7	9q34	+125270

* Acute intermittent porphyria is the most prevalent and 5-aminolevulinic acid–dehydratase deficient porphyria is the least prevalent of these diseases in the United States. ALA = 5-aminolevulinic acid (δ-aminolevulinic acid); HMB = hydroxymethylbilane; OMIM = Online Mendelian Inheritance in Man; PBG = porphobilinogen.
† Human Gene Mutation Database (www.hgmd.org) (21) as of 14 October 2004.
‡ Online Mendelian Inheritance in Man (for additional information on disease and its genetics) (www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).
§ Formerly known as uroporphyrinogen I synthase.

point at which the inherited partial enzyme deficiency becomes limiting, and intermediates accumulate in the liver. Porphobilinogen and ALA levels are increased in all patients with acute symptoms of these disorders and in some who are asymptomatic.

The cause of hepatic overproduction of porphyrin precursors in the acute porphyrias is better understood than are the mechanisms for neurologic damage. Presumably, symptoms result primarily from the porphyrin precursors themselves rather than a deficiency of heme in nerve tissue (26, 27). Chronic symptoms and signs may reflect previous, unresolved neurologic damage. In the very rare cases of homozygous acute intermittent porphyria (26), variegate porphyria (28), and hereditary coproporphyria (29), severe neurologic manifestations begin in childhood. An allogeneic liver transplantation in a woman with heterozygous acute intermittent porphyria normalized her urinary ALA and porphobilinogen levels in 24 hours and completely eliminated her recurrent neurologic attacks, which supports the hepatic overproduction of porphyrin precursors in causing the neurologic symptoms (27). Similarly, a patient with variegate porphyria manifested biochemical improvement after a liver transplantation for alcoholic cirrhosis (30). However, liver transplantation was not beneficial clinically or biochemically in a child with severe ALA-dehydratase porphyria (31). These important but limited case experiences help establish the role of the hepatic overproduction of heme precursors in causing neurologic manifestations of acute porphyrias but do not yet support the broad application of liver transplantation in these disorders.

Approximately 80% of carriers of a gene mutation for acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria remain asymptomatic, and others

Table 2. **Common Presenting Symptoms and Signs of Acute Porphyria***

Symptoms and Signs	Estimated Incidence, %	Comment
Gastrointestinal		
Abdominal pain	85–95	Usually unremitting (for hours or longer) and poorly localized but can be cramping. Neurologic in origin and rarely accompanied by peritoneal signs, fever, or leukocytosis.
Vomiting	43–88	Nausea and vomiting often accompany abdominal pain.
Constipation	48–84	May be accompanied by bladder paresis.
Diarrhea	5–12	
Neurologic		
Pain in extremities, back, chest, neck, or head	50–70	Pain may begin in the chest or back and move to the abdomen. Extremity pain indicates involvement of sensory nerves, with objective sensory loss reported in 10%–40% of cases.
Paresis	42–68	May occur early or late during a severe attack. Muscle weakness usually begins proximally rather than distally and more often in the upper than lower extremities.
Respiratory paralysis	9–20	Preceded by progressive peripheral motor neuropathy and paresis.
Mental symptoms	40–58	May range from minor behavioral changes to agitation, confusion, hallucinations, and depression.
Convulsions	10–20	A central neurologic manifestation of porphyria or due to hyponatremia, which often results from syndrome of inappropriate antidiuretic hormone secretion or sodium depletion.
Cardiovascular		
Tachycardia	28, 64–85	May warrant treatment to control rate, if symptomatic (see text).
Systemic arterial hypertension	36–55	May require treatment during acute attacks, and sometimes becomes chronic.

* Based on several series of patients with symptomatic acute intermittent porphyria (1, 4, 22–25).

Table 3. **Some Major Drugs Considered Unsafe and Safe in Acute Porphyrias***

Unsafe	Safe
Alcohol	Acetaminophen
Barbiturates†	Aspirin
Carbamazepine†	Atropine
Carisoprodol†	Bromides
Clonazepam (high doses)	Cimetidine
Danazol†	Erythropoietin§
Diclofenac and possibly other NSAIDs†	Gabapentin
Ergots	Glucocorticoids
Estrogens†‡	Insulin
Ethchlorvynol†	Narcotic analgesics
Glutethimide†	Penicillin and derivatives
Griseofulvin†	Phenothiazines
Mephenytoin	Ranitidine†§
Meprobamate (also mebutamate and tybutamate)†	Streptomycin
Methyprylon	
Metoclopramide†	
Phenytoin†	
Primidone†	
Progesterone and synthetic progestins†	
Pyrazinamide†	
Pyrazolones (aminopyrine and antipyrine)	
Rifampin†	
Succinimides (ethosuximide and methsuximide)	
Sulfonamide antibiotics†	
Valproic acid†	

* More extensive list of drugs and their status are available in texts (1) and Web sites (such as www.porphyriafoundation.com and www.porphyria-europe.com). NSAIDs = nonsteroidal anti-inflammatory drugs.
† Porphyria is listed as a contraindication, warning, precaution, or adverse effect in U.S. labeling for these drugs. For drugs listed as unsafe, absence of such cautionary statements in U.S. labeling does not imply lower risk.
‡ Estrogens have been regarded as harmful, mostly from experience with estrogen–progestin combinations and because they can exacerbate porphyria cutanea tarda. Although evidence that they exacerbate acute porphyrias is weak, they should be used with caution. Low doses of estrogen (e.g., transdermal) have been used safely to prevent side effects of gonadotropin-releasing hormone analogues in women with cyclic attacks.
§ Although porphyria is listed as a precaution in U.S. labeling, these drugs are regarded as safe by other sources.

may have only 1 or a few acute attacks throughout life. Levels of ALA, porphobilinogen, and porphyrins in urine, serum, and feces are normal in most asymptomatic carriers of autosomal dominant acute porphyrias. Moreover, most patients with ALA-dehydratase porphyria, who may have less than 5% of normal ALA dehydratase activity, also remain asymptomatic for most of their lives.

Common Clinical Features

Table 2 lists the most commonly reported clinical features of acute intermittent porphyria, which are identical in other acute porphyrias. Severe neuropathic abdominal pain, the most frequent symptom, is diffuse rather than localized and is often accompanied by nausea, vomiting, distention, constipation, and sometimes diarrhea. Other symptoms include insomnia (often an early symptom), heart palpitations, seizures (sometimes due to hyponatremia), restlessness, hallucinations, and other acute psychiatric symptoms. Hyponatremia may be due to hypothalamic involvement and inappropriate antidiuretic hormone secretion or excess gastrointestinal or renal sodium loss. Tachycardia and systemic arterial hypertension may correlate with increased catecholamine production. Sudden death, presumably from cardiac arrhythmia, may also occur during an acute attack (32, 33).

Peripheral neuropathy, which is primarily motor, usually develops in the setting of abdominal pain and other features of a severe acute attack. Pain in the extremities and elsewhere indicates sensory nerve involvement. Paresis is usually symmetrical and begins proximally in the upper extremities, but it may be focal and may involve cranial nerves. Weakness may progress to respiratory and bulbar paralysis and death, especially with delayed diagnosis. Even advanced paralysis is reversible with appropriate treatment but may require many months of rehabilitation.

Long-term complications include chronic arterial hypertension, renal impairment (34), chronic liver damage, and hepatocellular carcinoma (35–40). Some patients experience chronic neuropathic pain, which may account for an increased risk for depression and suicide (18).

Exacerbating Factors

Most exacerbating factors for acute porphyrias, including many drugs (**Table 3**), increase the demand for hepatic heme (particularly for cytochrome P450 enzymes) and induce ALA synthase. Many drugs cannot be classified as definitely harmful or safe because of insufficient information. Crash dieting (or other marked reductions in caloric or carbohydrate intake) is a common cause of attacks. Endogenous hormones, particularly progesterone, are important and may partially explain why attacks are more common in women and during the luteal phase of the menstrual cycle (41). Pregnancy is usually well-tolerated, but it increases attacks in some women. Cigarette smoking, which increases hepatic cytochrome P450 enzymes and presumably heme synthesis, is associated with more frequent attacks (42). Metabolic stress induced by infections or surgery, and possibly psychological stress, may lead to exacerbations. Attacks are usually due to the additive effects of several triggers, including some that are unknown.

Diagnostic Recommendations

Accuracy and speed are paramount in the diagnosis of an acute porphyric attack because delayed treatment can result in neurologic damage and even death. Rapid exclusion of acute porphyrias also avoids delay in establishing an alternative diagnosis.

When To Suspect an Acute Porphyric Attack

We recommend that acute porphyria be considered in any patient with symptoms that are prominent in these conditions, particularly abdominal pain, when initial clinical evaluation does not support another cause (see "Common Clinical Features" and **Table 2**). In our experience, acute porphyria is often seriously considered only after an expensive, time-consuming, and unproductive search for other abdominal conditions, including imaging studies and

Table 4. **Methods for Detecting Increased Urinary Porphobilinogen***

Method (Reference)	Feature	Principle of Test	Advantages	Disadvantages
Watson–Schwartz (43)	Qualitative	Separation of the PBG–Ehrlich's reagent pigment from other substances by organic solvent extraction	Rapid; reagents readily available	Lacks sensitivity; no reference standards; requires several extraction steps; false-positive results common†; does not measure ALA level
Hoesch (45)	Qualitative	Strong acid favors detection of the PBG–Ehrlich's pigment	Rapid; reagents readily available	Lacks sensitivity; no reference standards; false-positive results common†; does not measure ALA level
Mauzerall–Granick (44)	Quantitative	Anion and cation exchange resins separate PBG and ALA, respectively, from interfering substances, and ALA is reacted to form a pyrrole, before use of Ehrlich's reagent	Rapid, if done routinely; specific; measures both ALA and PBG levels; disposable columns available	Somewhat complex if done occasionally
Trace PBG Kit‡ (46)	Semi-quantitative	Anion exchange resin, as in the Mauzerall–Granick method	Rapid; specific; kit available	Does not measure ALA level

* ALA = 5-aminolevulinic acid (δ-aminolevulinic acid); PBG = porphobilinogen.
† False-positive results are especially common with inexperience.
‡ Thermo Trace/DMA, Arlington, Texas.

sometimes unnecessary surgery. Establishing or excluding the diagnosis through rapid, simple laboratory testing for porphobilinogen levels within hours of initial hospitalization, rather than after several weeks or longer, should be the goal.

Although a single characteristic symptom may lead to a diagnosis, additional features in a patient with abdominal pain might heighten the suspicion of an acute porphyria (for example, dark or reddish urine; new-onset hypertension; hyponatremia; proximal muscle weakness; pain associated with the luteal phase of the menstrual cycle; recent use of medications known to exacerbate porphyria; or low-calorie, low-carbohydrate diets). No single sign or symptom is universal, and 5% to 10% of patients may not have the most common features, abdominal pain and tachycardia. The family history may be unrevealing because most carriers of the trait in affected families are asymptomatic. However, patients with abdominal pain or other suggestive findings and a family history of acute porphyria should be tested immediately.

Because misdiagnoses of porphyrias are so common, a clinician should not assume that a history of porphyria in the patient or in the kindred is accurate. Laboratory results that were the basis for the initial diagnosis must be reviewed. If these are not available, the patient should be retested before hemin is administered. We recommend that patients with established acute porphyria wear medical alert bracelets, carry medical alert cards, and maintain records that include diagnostic laboratory reports to inform health care providers of their condition.

Recurrent attacks in a patient with proven acute porphyria are often similar over time and are diagnosed largely on clinical grounds. Biochemical reconfirmation is not required and treatment should be initiated immediately, after exclusion of other causes of symptoms (for example, pancreatitis and appendicitis).

Biochemical Testing

Urinary porphobilinogen level is substantially increased (20 to 200 mg/L) in patients with acute attacks of acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria. We recommend initial rapid testing for urinary porphobilinogen level to diagnose these most common acute porphyrias at or near the time of symptoms. Initial testing for a substantial increase in urinary porphobilinogen levels will miss the diagnosis of acute porphyria only in patients who are already receiving hemin, which can rapidly decrease ALA and porphobilinogen; the rare patient with ALA-dehydratase porphyria, which increases ALA but not porphobilinogen levels; and some cases of hereditary coproporphyria and variegate porphyria, because increases in ALA and porphobilinogen levels may be more transient in these conditions than in acute intermittent porphyria.

Most tests for porphobilinogen (**Table 4**) (43–46), a colorless pyrrole, rely on formation of a violet pigment with Ehrlich's reagent (*p*-dimethylaminobenzaldehyde) (2). Porphobilinogen must be separated from other urinary substances, principally urobilinogen, that also react with Ehrlich's aldehyde. The Mauzerall–Granick (44) and closely related methods are most reliable and are used for quantitative measurement of ALA and porphobilinogen levels. For rapid detection of increased porphobilinogen levels in urine, we recommend the Trace PBG Kit (Thermo Trace/DMA, Arlington, Texas), which detects porphobilinogen levels at concentrations greater than 6 mg/L and has a color chart for semi-quantitative estimation of higher levels (46).

During an acute attack of acute intermittent porphy-

Table 5. **Laboratory Findings That Differentiate Acute Intermittent Porphyria, Hereditary Coproporphyria, and Variegate Porphyria***

Disease	Erythrocyte Porphobilinogen Deaminase Levels	Urine Porphyrin Levels	Fecal Porphyrin Levels	Plasma Porphyrin Levels
Acute intermittent porphyria	Decreased by ~50% (in ~90% of cases)	Markedly increased, mostly uroporphyrin	Normal or slightly increased	Normal or slightly increased
Hereditary coproporphyria	Normal	Markedly increased, mostly coproporphyrin	Markedly increased, mostly coproporphyrin†	Usually normal
Variegate porphyria	Normal	Markedly increased, mostly coproporphyrin	Markedly increased, mostly coproporphyrin† and protoporphyrin	Markedly increased, characteristic fluorescence peak‡

* The findings listed are considered diagnostic for acute intermittent porphyria when porphobilinogen level is increased and for hereditary coproporphyria and variegate porphyria even when porphobilinogen levels may have returned to normal.
† Mostly coproporphyrin III (49, 50).
‡ A simple test, which consists of fluorescence scanning of diluted plasma at neutral pH, readily differentiates variegate porphyria from other porphyrias that cause elevated plasma porphyrin levels and cutaneous photosensitivity (47). A plasma porphyrin level determination is the most sensitive porphyrin measurement for detecting variegate porphyria, including asymptomatic cases (48).

ria, urinary excretion of porphobilinogen is generally 220 to 880 μmol/d (20 to 200 mg/d) (typical reference range, 0 to 18 μmol/d [0 to 4 mg/d]). Excretion of ALA (in μmol/d [mg/d]) is approximately half this amount (reference range, 0 to 53 μmol/d [0 to 7 mg/d]), since the molecular weight of ALA is half that of porphobilinogen. Because excretion of these porphyrin precursors is so high, differences in reference ranges between laboratories are of little consequence and collection of urine for 24 hours, which delays diagnosis, is unnecessary for the diagnosis of an acute attack. Urinary results expressed per gram of creatinine are readily compared with reference ranges for 24-hour excretion. Decreases occur with clinical improvement and are dramatic (but usually do not last long) after hemin therapy. After recovery from an attack of acute intermittent porphyria, levels of ALA and porphobilinogen generally remain increased, except immediately after hemin therapy or with prolonged latency. In hereditary coproporphyria and variegate porphyria, ALA and porphobilinogen levels may be less markedly increased and may decrease more rapidly after an acute attack than in acute intermittent porphyria, and excretion of ALA is more often similar to that of porphobilinogen (both expressed in mg). Recognition of ALA-dehydratase porphyria requires measurement of urinary ALA and porphyrin levels, since the porphobilinogen level is not significantly increased.

We recommend that all major medical facilities provide for in-house determination of urinary porphobilinogen levels within hours of obtaining the sample, preferably by using the Trace PBG Kit, because a delay of several days in testing may lead to life-threatening delay in diagnosis. The single-void urine sample should be refrigerated or frozen without additives and shielded from light for subsequent quantitative ALA, porphobilinogen, and total porphyrin determinations (which can detect hereditary coproporphyria or variegate porphyria when ALA and porphobilinogen levels have already decreased to normal). In patients with substantial renal dysfunction, ALA and porphobilinogen levels can be measured in serum.

If the porphobilinogen level is increased, second-line testing (**Table 5**) (47–50) will determine the precise disorder of porphyrin metabolism, although treatment (which is the same regardless of the type of acute porphyria) should not be delayed pending these results. If only the ALA level is substantially increased, ALA-dehydratase porphyria and other causes of ALA-dehydratase deficiency should be differentiated before treatment (1).

Biochemical Confirmation of the Type of Acute Porphyria

Acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria are readily differentiated, especially when clinically active, by a group of second-line tests (**Table 5**) that include measurement of erythrocyte porphobilinogen deaminase activity, as well as urine, plasma, and fecal porphyrin levels, measured in samples collected before beginning hemin therapy. Together, these tests will also identify rare cases of dual porphyria (with deficiencies of 2 enzymes in the heme pathway). Marked increases in urinary and fecal total porphyrin levels and relative, rather than absolute, amounts of the individual porphyrins (separated by high-performance liquid chromatography or thin-layer chromatography) are of greatest diagnostic importance. Therefore, spot urine and fecal samples are suitable for second-line testing. Total plasma porphyrin levels are best measured fluorometrically either by acidification and solvent extraction or in diluted plasma at neutral pH (47).

We emphasize that relying on these second-line tests is not warranted for initial diagnosis of an acutely ill patient before treatment because they lack sensitivity, specificity, or both. Urinary porphyrin levels, for example, can be increased in many nonporphyric conditions. Coproporphyrin is the predominant porphyrin in normal urine, but it is also partially excreted in bile. Even minor liver dysfunction may reduce biliary and thus increase urinary coproporphyrin excretion. Therefore, increased urinary coproporphyrin does not always signify a disturbance in heme synthesis.

A substantial increase in ALA level with a normal porphobilinogen level suggests ALA-dehydratase porphyria.

However, further evaluation is needed to exclude other causes of ALA-dehydratase deficiency, particularly lead poisoning and hereditary tyrosinemia type I, which can produce symptoms similar to acute porphyria. In ALA-dehydratase porphyria and other ALA-dehydratase deficiency diseases, urinary coproporphyrin III and erythrocyte zinc protoporphyrin levels are also increased. Increased porphyrin levels seen in ALA-dehydratase porphyria and acute intermittent porphyria may result from metabolism of excess ALA in tissues other than the liver. Clinicians should confirm ALA-dehydratase porphyria by using both enzymatic and molecular methods.

Enzymatic and DNA Testing

We recommend enzyme activity measurement and DNA testing to help confirm the type of acute porphyria and to enable identification of asymptomatic but at-risk relatives. Half-normal activity of erythrocyte porphobilinogen deaminase helps confirm a diagnosis of acute intermittent porphyria in patients with increased porphobilinogen. This assay is useful for screening family members once an index case has been identified. However, normal erythrocyte porphobilinogen deaminase activity does not exclude acute intermittent porphyria because some mutations in the porphobilinogen deaminase gene lead to a deficiency of the enzyme in the liver and other organs but not in erythrocytes (1, 25). A definitive diagnosis may also be precluded because 1) the normal range for erythrocyte porphobilinogen deaminase activity is wide (up to 3-fold) and low-normal and high-carrier values overlap; 2) the enzyme activity is much higher in younger than older erythrocytes and therefore increases when erythropoiesis is stimulated; and 3) improper processing, storing, and shipping of blood samples can decrease enzyme activities.

Assays of the enzymes deficient in hereditary coproporphyria and variegate porphyria are technically difficult and must be performed in extracts of cells with mitochondria, such as lymphocytes or cultured fibroblasts. These assays are available in many European reference laboratories but not in North America.

Once biochemical studies have determined the type of acute porphyria, DNA studies can identify the disease-causing mutation or mutations in the defective gene. This permits rapid and accurate testing of asymptomatic at-risk family members by DNA studies. (Mutation analysis for patients with acute porphyria and their family members is available at the Mount Sinai School of Medicine, Department of Human Genetics, New York, New York. Contact Dr. Kenneth Astrin [kenneth.astrin@mssm.edu] for information.) Most mutations are family-specific, with a few notable exceptions, including variegate porphyria in South Africa (51) and acute intermittent porphyria in northern Sweden (52), where particular mutations have been transmitted over generations from single founders.

Patients with porphyria should have genetic counseling and should be encouraged to inform family members about the disease and its genetics. Knowledge of genetic status enables family members to make informed decisions about lifestyle and to know the potential risks of certain drugs, preferably before the development of an acute illness. However, latent porphyria should not be construed as a health risk that limits health or life insurance. Acute porphyria may be diagnosed prenatally with enzymatic and molecular studies, but this is seldom indicated because the outlook for most carriers is favorable.

THERAPEUTIC RECOMMENDATIONS

Acute attacks require treatment of symptoms and complications and disease-specific therapy (that is, intravenous hemin) to reconstitute heme homeostasis (see Key Summary Points and **Figure**).

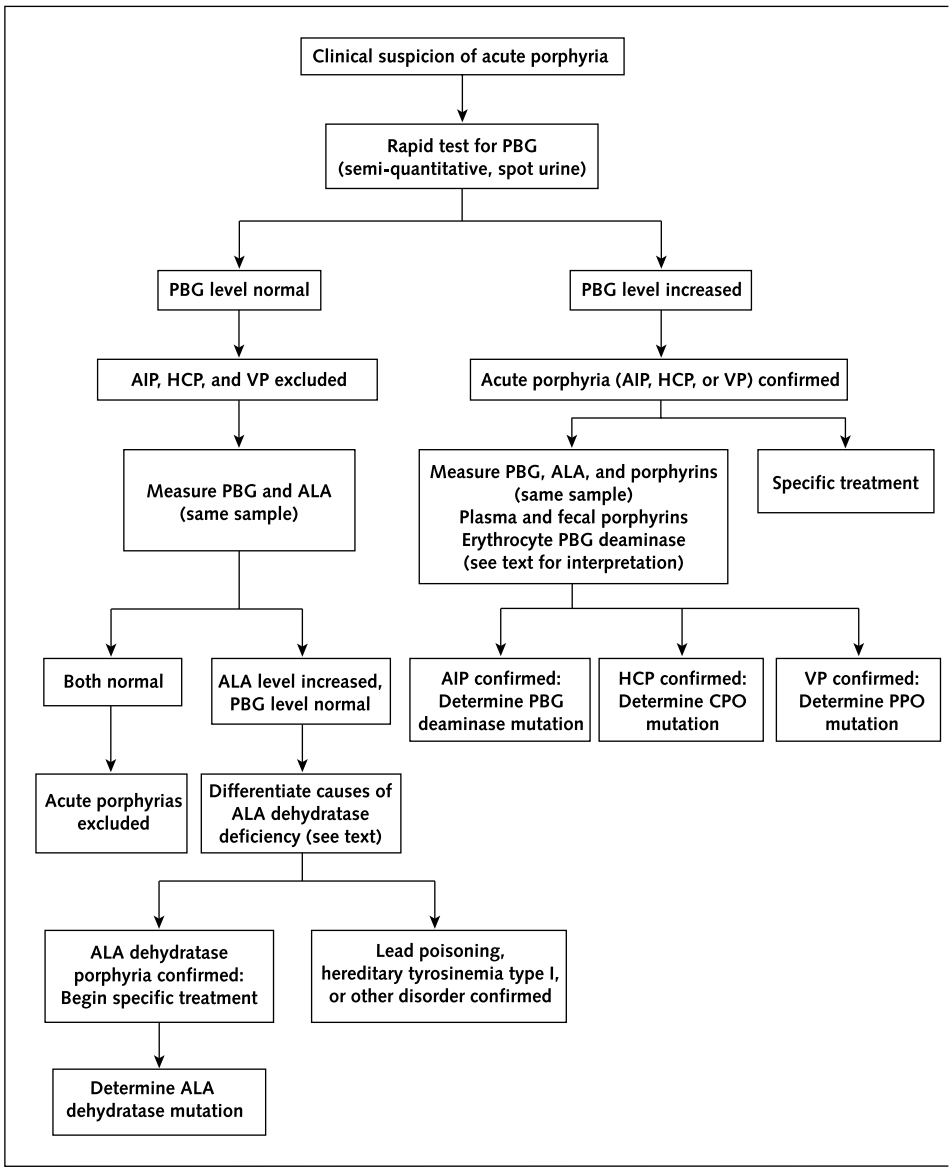
Supportive and Symptomatic Treatment

Hospitalization may be required for evaluating and treating severe pain, nausea, and vomiting; for administering intravenous fluids, electrolytes, glucose, and hemin; and for closely observing electrolyte derangements and neurologic complications. Medications taken by the patient should be reviewed immediately, and those identified as harmful should be stopped if possible. Narcotic analgesic drugs are usually required for abdominal pain, and small to moderate doses of a phenothiazine are indicated for nausea, vomiting, anxiety, and restlessness. The Key Summary Points contain other management considerations.

Early case studies suggested that oral or intravenous carbohydrate loading may benefit some patients (53, 54). Carbohydrate loading provides nutritional replacement, has some repressive effect on hepatic ALA synthase (55, 56), and has been a standard treatment for acute attacks for many decades. While less effective and specific than hemin, carbohydrate loading may suffice for mild attacks in patients with low narcotic requirements and without hyponatremia or paresis. Sucrose, glucose polymers, or carbohydrate-rich foods may be given to patients without abdominal distention or ileus and who can tolerate oral treatment. The standard intravenous regimen is 10% glucose for a total of at least 300 g daily. Amounts up to 500 g daily may be more effective (57). However, large volumes of 10% glucose may increase risk for hyponatremia. Severe or prolonged attacks should be treated with hemin and may also require more thorough nutrition support.

Tachycardia and systemic arterial hypertension may be treated cautiously with β-adrenergic blocking agents, but they may be hazardous in patients with hypovolemia, in whom increased catecholamine secretion may be an important compensatory mechanism. Seizures are difficult to treat because almost all antiseizure drugs can exacerbate an attack. Gabapentin, and probably vigabatrin, can be given safely and benzodiazepines are relatively safe. Careful correction of hyponatremia and hypomagnesemia is impor-

Figure. **Recommended laboratory evaluation of patients with concurrent symptoms suggesting an acute porphyria, indicating how the diagnosis is established or excluded by biochemical testing and when specific therapy should be initiated.**



This schema is not applicable to patients who have recently been treated with hemin or who have recovered from past symptoms suggestive of porphyria. Levels of 5-aminolevulinic acid (*ALA*) and porphobilinogen may be less increased in hereditary coproporphyria (*HCP*) and variegate porphyria (*VP*) and decrease more quickly with recovery than in acute intermittent porphyria (*AIP*). Mutation detection provides confirmation and greatly facilitates detection of relatives with latent porphyria. CPO = coproporphyrinogen oxidase; PBG = porphobilinogen; PPO = protoporphyrinogen oxidase.

tant, particularly when those conditions are associated with seizures.

Hemin Therapy

Intravenous hemin addresses the underlying pathophysiology by repressing hepatic ALA synthase activity, hence decreasing the overproduction of ALA and porphobilinogen. Hemin given intravenously at moderate dosage (3 to 4 mg/kg of body weight per day) is mostly taken up in the liver and can at least transiently replenish the depleted heme pool that regulates the synthesis of ALA synthase. It cannot be given orally because it is catabolized by heme oxygenase during intestinal absorption.

Many uncontrolled clinical studies suggest a favorable biochemical and clinical response to hemin (5–8, 10, 13, 16, 17, 19, 58–60). In the only double-blind, placebo-controlled trial of hemin therapy, investigators randomly assigned 12 patients with acute porphyria to receive either hemin (as heme arginate) or placebo (12). The 9 patients who were readmitted with a subsequent attack received the therapy that they did not get during the earlier attack. This study found striking decreases in urinary porphobilinogen excretion and trends in clinical benefit (less pain, decreased need for pain medication, and shorter hospital stay) associated with hemin. However, notably, the study lacked

statistical power, treatment was delayed for 2 days in all cases, clinical assessments were limited, and information on what precipitated the attack (which could affect the likelihood of spontaneous remission in either group) was not recorded (18, 61, 62). In a larger, uncontrolled study of 22 patients and 51 acute attacks treated with heme arginate, treatment was initiated within 24 hours of admission in 37 attacks (73%). All patients responded (including 2 patients with paresis), and hospitalization was less than 7 days in 90% of cases (16). In general, early initiation of intravenous hemin is associated with improved outcome (10, 16, 17, 59), and hemin is more effective than glucose in reducing excretion of porphyrin precursors (3, 6, 7).

Hemin therapy should be started early for most acute attacks (16, 59, 63–66). Although product labeling recommends an initial trial of intravenous glucose, hemin is the preferred therapy (16, 59, 63–66). Glucose is clearly less effective and is recommended only for attacks with mild pain and no paresis. The standard regimen for hemin therapy is 3 to 4 mg/kg infused intravenously once daily for 4 days. Hemin (Panhematin, Ovation Pharmaceuticals, Deerfield, Illinois) is available in the United States as lyophilized hydroxyheme (hematin) for reconstitution with sterile water just before infusion and is approved by the FDA for ameliorating acute porphyric attacks. A standard 4-day treatment course costs approximately $8000. Another hemin preparation, heme arginate, is more stable in solution but is not available in the United States. We recommend that lyophilized hemin be reconstituted with human albumin to enhance stability (60). Degradation products form rapidly in vitro when lyophilized hemin is reconstituted with sterile water, as recommended in product labeling. These degradation products adhere to endothelial cells, platelets, and coagulation factors and cause a transient anticoagulant effect and often phlebitis at the site of infusion (67–71). Phlebitis can be severe and can compromise venous access with repeated administration. In our experience, reconstitution with albumin enhances stability of lyophilized hemin, decreases the incidence of phlebitis, prevents the anticoagulant effect, and may enhance efficacy (60), although it increases the cost of treatment. Other uncommon reported side effects of hemin include fever, aching, malaise, hemolysis, 1 case of circulatory collapse that resulted in full recovery after subsequent hemin infusions (72), and 1 case of transitory renal failure after a dose of 1000 mg (73). Experience indicates that hemin can be administered safely during pregnancy.

Patients should be monitored closely during therapy for complications and signs of progression of acute porphyria, such as electrolyte imbalance, acute psychiatric manifestations, muscle weakness, bladder retention, and ileus. Spirometry is sometimes indicated daily to detect respiratory impairment, at least until the attack begins to resolve. Since patients with respiratory impairment can deteriorate rapidly, we recommend that they be placed in intensive care. Levels of ALA and porphobilinogen usually decrease to normal whether therapy is started early or late, but this does not necessarily predict a clinical response.

Clinical improvement is rapid, often within 1 to 2 days, when hemin therapy is started early in an attack. Patients may be discharged from the hospital within several days, although we recommend completion of the standard 4-day treatment course in the outpatient clinic. But when treatment is delayed, neuronal damage may be advanced and slow to recover. Therefore, efficacy of hemin may not be immediately apparent, and treatment for longer than 4 days should be considered, although evidence that this improves outcome is lacking. Even when severe neuropathy is arrested by treatment, complete recovery may take months or longer. Hemin is seldom effective for chronic symptoms that persist between attacks. Hemin therapy can be given in outpatient settings or in the home if this facilitates prompt therapy and reduces medical care costs in patients with frequent attacks.

Recommendations for Prevention and Follow-up

Prevention of future attacks requires patient education and identification of precipitating factors. Avoiding alcohol, smoking, and drugs that can induce exacerbations and maintaining adequate nutrition (**Table 3**) are important. Medical alert bracelets and wallet cards can help notify emergency medical personnel and ensure that unsafe drugs are not given to patients in emergencies. Some patients have frequent attacks even after exacerbating factors are removed, possibly because of unidentified modifier genes or environmental or endogenous precipitating factors. These patients should be evaluated by a nutritionist and should follow a well-balanced diet with sufficient calories to maintain weight.

Gonadotropin-releasing hormone analogues can be highly effective for women with frequent cyclic attacks when symptoms are confined to the luteal phase of the menstrual cycle (41). Unless patients have other medical indications for oophorectomy, a trial of a gonadotropin-releasing hormone analogue is preferred because it is reversible. Therapy should be started during the first few days of a cycle, and if attacks are prevented for several months, estrogen, added back in the form of a low-dose estrogen patch, can prevent menopausal symptoms. We recommend gynecologic examination and bone density determinations every 6 months during treatment. Continued need can be assessed every 1 to 2 years by stopping treatment.

Pregnancy increases levels of progesterone, a potent inducer of heme biosynthesis in liver, but nevertheless is well tolerated in most women with acute porphyria. For example, in a large series of women with acute intermittent porphyria or variegate porphyria who had 176 deliveries, porphyric symptoms were absent in 92% of these pregnancies (74). Because some women experience more frequent

attacks during pregnancy, counseling women who wish to become pregnant must be individualized. Worsening symptoms during pregnancy are sometimes due to harmful drugs (for example, metoclopramide) (75, 76), inadequate nutrition, or both.

Recurrent noncyclic attacks are sometimes prevented by weekly or biweekly infusions of hemin (77). Frequent treatment with hemin has a theoretical risk for iron overload (100 mg of hemin contains 8 mg of iron). Therefore, serum ferritin levels should be monitored. In selected, rare instances of severe, unremitting symptomatic disease, orthotopic liver transplantation may be considered (28). Transplantation of hepatocytes or specific gene replacement therapy are possible future therapeutic strategies.

End-stage renal disease may partly result from chronic systemic arterial hypertension (34) and may be delayed by effective blood pressure control. Several retrospective population-based studies in Scandinavia have found 60- to 70-fold increases in incidence of or mortality due to hepatocellular carcinoma among patients with acute porphyria as compared with national age- and sex-matched rates (36–38, 40). In addition, a prospective cohort study of 650 patients with acute porphyria followed for 7 years in France found 7 cases of hepatocellular carcinoma versus an expected 0.2 case as determined by national age- and sex-specific incidences of primary liver cancer (39). Thus, as with other conditions that predispose to liver cancer, periodic monitoring of serum α-fetoprotein levels and hepatic imaging seems appropriate. Chronic depression and risk for suicide (18) are important to recognize in patients with frequent attacks or chronic symptoms and should prompt early psychiatric and effective pain management.

IMPROVING PROGNOSIS

Reported fatality rates from acute attacks of porphyria ranged from 10% to 52% before 1970 (4, 78). Improved prognosis since 1970 may be attributed to better diagnosis, treatment, and prevention; availability of hemin (introduced in 1971); identification of at-risk gene carriers; and decreased use of harmful drugs, such as barbiturates and sulfonamide antibiotics. In a more recent U.S. study, 12 of 86 patients (14%) who received a diagnosis after 1971 died after hospitalization for acute attacks. Eleven of these patients received hemin but only after their attack had progressed to an advanced stage, with 10 patients requiring mechanical ventilation (18). Studies have estimated mortality in patients who have experienced attacks of acute porphyria to be 3-fold higher than the general population, with most deaths occurring during acute attacks (18) and delayed diagnosis and treatment still often contributing (18, 74). The Key Summary Points are intended to increase awareness of these disorders, encourage earlier and more accurate diagnosis, and suggest the earlier institution of specific therapy, with the aim of further enhancing prognosis of patients with these inherited conditions.

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