



# Acute Intermittent Porphyria (AIP)

## OVERVIEW

AIP is the most common of the AHPs, with a world-wide prevalence of clinically manifest, symptomatic disease of approximately 5-10 per 100,000. AIP results from autosomal dominant inheritance of a mutation in the gene for the enzyme hydroxymethylbilane-synthase (HMBS), which is also known as porphobilinogen deaminase (PBGD) or uroporphyrinogen I synthase. Evidence both from Europe and the USA indicates that potential disease-causing mutations in the HMBS gene are far more common than previously believed; in those of western European ancestry, the prevalence of such mutations is about 1/1700. These observations emphasize that the enzyme deficiency alone is not sufficient to produce the symptoms of AIP; other factors, such as gender, menarche/puberty, drugs, hormones, excess alcohol use, smoking, dietary factors, and/or other genetic factors are also important. Sometimes, triggering factors cannot be identified.

## SYMPTOMS

Most people who have a potential disease-causing mutation in the HMBS gene never develop symptoms; this is referred to as “latent” AIP. Symptoms rarely develop prior to puberty, and the clinical disease is mainly seen in women (~ 90% of symptomatic patients) in their child-bearing years (ages ~18-50 years). However, symptoms can also present in men. Acute attacks almost always start with pain in the abdomen but sometimes in the chest, back, or thighs, and are often accompanied by nausea, vomiting, and constipation. The severity of the pain typically escalates over a few hours; it may become very severe and be described as the worst pain someone has ever experienced. During acute attacks, heart rate and blood pressure are commonly increased. These symptoms and signs are all due to the effects of the disease on the nervous system—autonomic, peripheral, and central. Confusion, convulsions, and muscular weakness, due to impairment of the nerves controlling the muscles, may lead to paralysis. A full-blown acute attack usually gradually develops and escalates over hours and lasts for days or weeks. Recovery from severe paralysis is generally slow and often incomplete, with residual wrist drop or foot drop. The skin is not affected, except in some AIP patients who have developed kidney failure, in whom plasma levels of uroporphyrin may increase due to impaired renal clearance. If the disease is already known or is diagnosed promptly early in the clinical course of an acute attack, both the severity and duration of the attack can be much diminished by prompt and appropriate treatment.

## TRIGGERS

Acute attacks are often provoked by drugs that induce hepatic cytochromes P-450, such as barbiturates, anti-seizure drugs (barbiturates, hydantoins, valproate), rifampin, metoclopramide, and excess alcohol. Attacks in women may occur after ovulation and during the second half [luteal phase] of the menstrual cycle when progesterone levels are high. Reduced food intake, often in an effort to lose weight, as well as infections, surgery, and stressful situations may also precipitate attacks.





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### SYMPTOM FREQUENCY

Many patients with AHPs never experience acute attacks (called latent). They may go through their lives without adverse symptoms or signs. Such patients, if diagnosed at all, have the diagnosis made because of first-degree relatives with symptomatic disease that leads to family testing. Some patients have only a few attacks in their lifetimes, while others can have frequent attacks. Less than 4 attacks per year are classified as sporadic, while >4 per year are classified as recurrent.

### LONG TERM COMPLICATIONS

Risks for developing systemic arterial hypertension, chronic renal disease, and liver cancer (hepatocellular carcinoma) are increased in AIP. Anxiety and depression may be chronic issues in the AHPs.

### TREATMENT & PROGNOSIS

The prognosis is usually good if the disease is recognized and if treatment is prompt, before severe nerve dysfunction develops. Although acute symptoms usually resolve after an attack, repair of nerve damage and associated muscle weakness may require several months or longer. Mental symptoms, like hallucinations, may occur during attacks but are not chronic.

Hospitalization is often necessary for acute attacks. Medications for pain, nausea, and vomiting and close observation are generally required. Hyponatremia, sometimes severe, with serum Na < 125 mEq/L, and hypomagnesemia are not uncommon during acute attacks. During treatment of an attack, attention should be given to sodium and water balance and to repletion of magnesium. Harmful drugs should be stopped.

For all patients with acute attacks who are sick enough to require hospital admission, hemin therapy should be started as quickly as possible. Hemin must be administered intravenously. Panhematin is the only hemin preparation available in the United States. Panhematin is more stable and less likely to produce phlebitis (a known possible side effect of hemin) if it is reconstituted in human serum albumin before it is given. Because of the high frequency of thrombophlebitis, Panhematin is best given into a large-bore, high-flow central vein, such as a subclavian vein, either by PICC line or by a central port. Normosang, which is heme arginate, is available in most European and some other countries around the world. Although Panhematin® or Normosang have few side effects, they do act as mild anticoagulants. Thus, concurrent use of other anticoagulants such as heparin or Coumadin® (warfarin) should be avoided. Harmful drugs, which can be identified using online drug databases, should be discontinued immediately.

Recurrent attacks related to the menstrual cycle can possibly be prevented by a gonadotropin-releasing hormone (GnRH) analogue administered with expert guidance. In selected cases, frequent attacks can be prevented by prophylactic infusions of hemin, which are titrated to patient response. A newer alternative for prevention of frequent, recurrent acute attacks is the subcutaneous administration of givosiran (Givlaari).





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### MANAGEMENT

Attacks can be prevented in many cases by avoiding known triggers including certain medications, alcohol, stress, smoking, illicit drugs, exogenous hormones and hypocaloric diet or fasting.

Patients with chronic kidney disease should have regular monitoring with a nephrologist. HCC surveillance with liver ultrasound or other imaging every 6 months, is recommended starting at the age of 50 years old for early detection. The risk of development of HCC is likely greater among patients with chronically elevated levels of ALA and PBG in serum and urine. Additionally, Hepatitis B and A vaccines are recommended to avoid preventable infections of the liver.

Liver transplantation has been shown to be an effective treatment for AIP patients with frequent and severe recurrent attacks who were resistant to conventional treatment including Panhematin®. However, experience with this treatment modality is still limited. It is anticipated that the need for liver transplantation for AHP will decrease now that givosiran has become available for use by at least some patients with frequent recurrent attacks. Givosiran (Givlaari) has proven effective in decreasing the frequency and severity of acute attacks, and it generally is reasonably well-tolerated.

### DIET

Individuals with AIP who are prone to attacks should eat a normal or high carbohydrate diet and should not greatly restrict their intake of carbohydrate and calories, even for short periods of time. If weight loss is desired, it is advisable to consult a physician and a dietitian to have them prescribe and oversee an individualized diet that is not more than 20% below the normal level of calories for the patient. This should result in a gradual weight loss and usually will not cause an attack of porphyria. Gastric bypass surgery for obesity has occasionally led to first attacks of AHP.

### PREGNANCY

Pregnancy is usually well tolerated, but the hormonal changes may exacerbate AIP in some women. Proper nutrition and hydration are important during pregnancy and labor, after delivery, and for the duration of breastfeeding. Only drugs and anesthetics classified as safe in the AHPs should be used. Acute attacks are treated with hemin; there is no evidence of adverse effects of hemin therapy on the mother or fetus. Little, if any, heme, bound to hemopexin or albumin in the serum, is taken up across the placenta into the developing fetus. Patients are prone to more frequent and severe attacks in the post-partum period, as well as during pregnancy. IV hemin can be given also to mothers who are breast-feeding, if required, without fear of adverse effects on their infants.





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### PREVENTION

Attacks can be prevented in many cases by avoiding alcohol excess, smoking, harmful drugs and dietary practices. Wearing a Medic Alert bracelet and carrying a Medic Alert card is advisable for patients who have had attacks, but is probably not warranted in most latent cases. Very frequent premenstrual attacks can possibly be prevented by a gonadotropin-releasing hormone (GnRH) analogue administered with expert guidance. In some cases, frequent, cyclic attacks can be prevented by periodic (weekly, biweekly, etc.) infusions of hemin.

A newer alternative for prevention of frequent, recurrent acute attacks is the subcutaneous administration of givosiran (Givlaari). It is administered subcutaneously once per month, and it has generally been well-tolerated and highly effective. IV hemin can still be used, as may be required, in persons receiving givosiran.

Patients with severe renal disease tolerate hemodialysis or kidney transplantation. It is important that such patients still have adequate functional status at the time of kidney transplantation. Those with severe malnutrition and/or neurological deficits are at high risk of poor outcomes after kidney transplantation.

Liver transplantation has been very effective for patients with classical AIP who have repeated attacks and who are resistant to other treatments. However, experience with transplantation as a treatment for AIP is still limited.

### FAMILY TESTING & COUNSELING

Because AIP is an autosomal dominant disorder, persons with disease-associated mutations in the HMBS gene have a 50% chance with each pregnancy of passing that mutation on to their offspring. The outlook for such offspring is generally good, since most individuals who inherit an HMBS gene mutation never develop symptoms of AIP.

Knowing the mutation that causes AIP in a particular family member means that others who carry the mutation can be reliably identified and counseled to avoid excess alcohol, drugs, dietary practices, etc. that may trigger symptoms.

### HOMOZYGOUS FORM

An ultra-rare form of homozygous AIP can occur when two HMBS mutations are present on both copies of the gene. This form is severe and presents in early childhood with neurological symptoms. Only a handful of cases have been reported.

### References

1. Balwani M, et al. Acute hepatic porphyrias: Recommendations for evaluation and long-term management. 2017.
2. Bonkovsky HL, Dixon N, Rudnick S. Pathogenesis and clinical features of the acute hepatic porphyrias (AHPs). 2019

