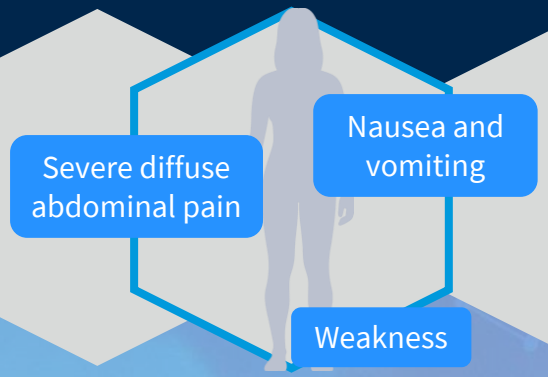
Accurate, Prompt Diagnosis of AHP is Essential to Reduce the Risk of Serious Chronic and Acute Disease Complications[1,2]

Click on '⊕' to learn more

Diagnostic Scenario*

40-year-old female presents with…



These key clinical features should raise suspicion of AHP[2]

Note that not all patients will appear with severe diffuse abdominal pain.[3]

- Patients with key clinical features should be considered for AHP screening, including AIP which corresponds to ~80% of AHP cases[4,5] ⊕
- AHP is a group of rare diseases with variable presentation and non-specific manifestations[1] ⊕
- Diagnosis of AHP is frequently delayed, with an average of 15 years from onset of symptoms to diagnosis[6] ⊕
- Undiagnosed AHP is associated with significant patient burden and can lead to serious long-term complications[2] ⊕

Once suspected, appropriate testing can help diagnose AHP[2]

AGA Clinical Practice Update[4] → Symptoms suggestive of AHP → **Spot urine** for ALA, PBG, creatinine[†,‡] → Urine ALA/PBG >10 mg/g creatinine[§] → AHP confirmed → **Genetic testing** to determine AHP type

Early and accurate diagnosis of AHP starts with:

- An **accurate history**
- First-line screening **biochemical tests**
- Confirmatory **genetic testing** if first-line testing is abnormal[7]

Biochemical testing measuring ALA, PBG, and Cr in a random urine sample[4] ⊕

Urine ALA/PBG normal → AHP excluded as cause of symptoms

Genetic testing should be used to confirm the AHP type or for screening of individuals with a first-degree family member with AHP[4] ⊕

*Hypothetical case; †Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic;[4] ‡During acute attacks, both ALA and PBG are elevated at least 5-fold the ULN;[4] §If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia.[4]

⊕ Click for abbreviations and references

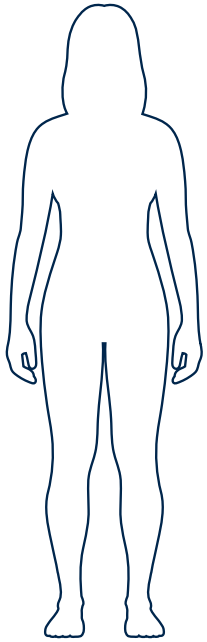
Intended for US HCPs

Scan the QR code to learn more on the RNAi Science website

October 2024 | MED-US-AS1-2400024

Consider AHP in Any Patient, Especially Any Woman of Childbearing Age, Who Presents with Unexplained Recurrent, Severe Abdominal Pain[4,*]

Patient Profile



Age of onset of clinical manifestation varies, but the majority of patients are aged 15–50 years at onset[4,8]

Women are predominantly affected[4,9]

~1 in 1600–1700
Mutation prevalence of the most common type of AHP, AIP[10,11]

~1%
Estimated phenotypic penetrance of symptomatic disease among AIP gene carriers[4]

~10 in 1,000,000
People diagnosed with symptomatic AIP in the US[12]

*Note that not all patients will appear with severe diffuse abdominal pain.[3]

Click for abbreviations and references

Key Symptoms of AHP That Should Prompt Referral for Testing Include Severe Diffuse Abdominal Pain, Nausea, and Vomiting

AHP is characterized by chronic symptoms, acute attacks, and long-term complications[13–16]

As a multi-system disease, AHP does not fall under the responsibility of a single medical specialty[1]

Pick your speciality to learn more about the common presenting symptoms of AHP:

- Hepatology
- Hematology
- Gastro-enterology
- Neurology
- Psychiatry
- Other

Click for abbreviations and references

Key Symptoms of AHP Which Should Prompt Referral for Testing Include Severe Diffuse Abdominal Pain, Nausea, and Vomiting[1,3,13]

Symptoms experienced by patients with AHP*,†

Gastrointestinal symptoms
- ✓ **Nausea**
- ❑ Constipation
- ✓ **Loss of appetite**
- ✓ **Vomiting**[A]
- ❑ Heartburn

Mood or sleep symptoms
- ✓ **Tiredness**
- ❑ Trouble sleeping
- ❑ Anxiety
- ❑ Trouble concentrating
- ❑ Feeling unmotivated[C]
- ❑ Hallucinations

Pain symptoms
- ✓ **Abdominal pain**
- ❑ Arm/leg pain
- ❑ Back pain
- ❑ Muscle pain
- ❑ Headache
- ❑ Other pain

Other symptoms
- ✓ **Changes in urine color**
- ❑ Weakness
- ❑ Numbness
- ❑ Fast heartbeat
- ❑ Sweating[A]
- ❑ Blisters/rashes

All symptoms can be both acute and chronic unless otherwise stated.
[A]Acute symptom only; [C]Chronic symptom only.

Hepatologist

As a hepatologist, consider **symptoms of hepatic disorder** in **blue** in your patients that may be **suggestive of AHP**

Take a moment to consider **the other symptoms of AHP**:
- Does your patient have any other symptoms that match the AHP symptom profile?
- Does your patient fit the AHP patient profile?

If yes, consider testing for AHP as a **differential diagnosis**

*These are not all the symptoms of AHP; †Frequently reported acute symptoms (≥50%) by patients during an attack at baseline and most commonly reported chronic symptoms (proportion of patient reporting chronic symptoms at baseline n=73) in EXPLORE-A (N=112)[3]

Click for abbreviations and references

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Hematologist

As a hematologist, consider **symptoms** in your patients that may be **suggestive of AHP**

- Does your patient fit the AHP patient profile?

If yes, consider testing for AHP as a **differential diagnosis**

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Gastroenterologist

As a gastroenterologist, consider **GI symptoms** in **blue** in your patients that may be **suggestive of AHP**

Take a moment to consider **the other symptoms of AHP**:
- Does your patient have any other symptoms that match the AHP symptom profile?
- Does your patient fit the AHP patient profile?

If yes, consider testing for AHP as a **differential diagnosis**

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Neurologist

As a neurologist, consider **neurological symptoms** in **blue** in your patients that may be **suggestive of AHP**

Take a moment to consider **the other symptoms of AHP**:
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- Does your patient fit the AHP patient profile?

If yes, consider testing for AHP as a **differential diagnosis**

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Psychiatrist

As a psychiatrist, consider **psychological symptoms** in **blue** in your patients that may be **suggestive of AHP**

Take a moment to consider **the other symptoms of AHP**:
- Does your patient have any other symptoms that match the AHP symptom profile?
- Does your patient fit the AHP patient profile?

If yes, consider testing for AHP as a **differential diagnosis**

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Identifying Symptoms

Consider **symptoms** in your patients that may be **suggestive of AHP**

- Does your patient fit the AHP patient profile?

If yes, consider testing for AHP as a **differential diagnosis**

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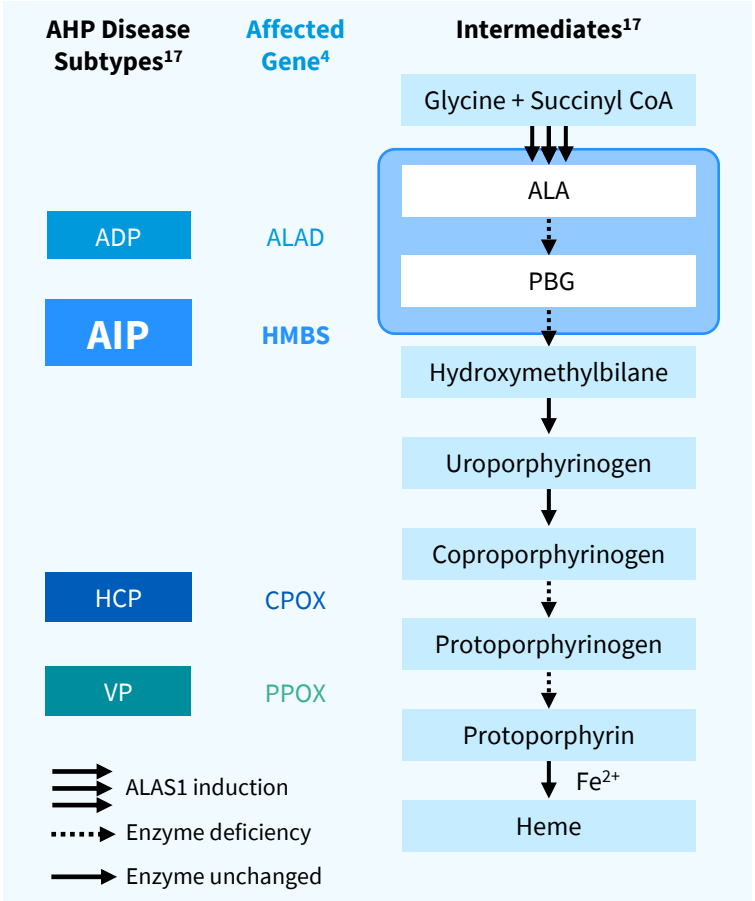
Click for abbreviations and references

AHP Arises from Genetic Variants that Disrupt the Heme Biosynthesis Pathway



Neurotoxic accumulation[15,16]

AHP pathophysiology

- Triggers induce heme synthesis through ALAS activation[19]
- Resulting accumulation of toxic heme metabolites, leading to symptoms in several organ systems[19]

Severe, diffuse pain in abdomen, chest, back[1,18,20]

Weakness, numbness, respiratory failure[1,18,20]

Confusion, anxiety, seizures, hallucinations[1,18,20]

Click for abbreviations and references

Characteristics of AHP Types

AHP Type[21]	Sex[21]	Age of Onset	Typical Presenting Symptoms[21]		Estimated % of AHP
			Acute Attacks	Cutaneous	
AIP	Symptomatic patients are predominantly female[21–23]	15–50 years[4,8]	✓		**Most prevalent** ~80%[5]
VP			✓	✓	Less prevalent[24]
HCP			✓	✓	Less prevalent[24]
ADP	All recorded symptomatic patients have been male[21]	Variable[19]	✓		**Least prevalent** 12 cases ever reported worldwide[25]

Click for abbreviations and references

Delayed Diagnosis Can Negatively Impact Patient Morbidity and Mortality

Patients often **present to emergency departments** where less common causes of typical AHP presenting symptoms (e.g. abdominal pain) are often not considered[1]

Patients report **frequent hospitalizations and visits to multiple specialists before diagnosis**, with many being labelled as "drug seekers" because of their recurrent need for pain relief[2]

"Very few doctors understand what porphyria is or even how to treat it" *Patient with AHP*[5]

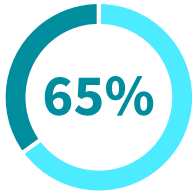
"I have to take all these stupid medications, and there's so much stigma in society about prescription pain meds" *Patient with AHP*[5]

Many patients experience delays in diagnosis or misdiagnosis, resulting in **inappropriate or harmful treatments**, including certain medications that can upregulate the heme biosynthesis pathway and **worsen AHP symptoms**[1]

Inaccurate diagnoses may also result in **ineffective surgical interventions**, for example appendectomy or hysterectomy[4]

Click for abbreviations and references

Patients with AHP Can Experience an Array of Chronic Symptoms, Which Fluctuate in Severity, Alongside Acute Attacks Resulting in Hospitalization Which Leads to High Disease Burden[3,5]



65% of patients with recurrent attacks experience chronic symptoms, most commonly pain, tiredness, anxiety, and nausea, with 46% of patients experiencing these symptoms daily[3,*]

"When it's chronic, it's something I'm **constantly having to manage**… there will be pains where I feel like I'm getting **stung by a swarm of bees** or something like that. But it doesn't get to the point where I'm having to go to the emergency room and vomiting"[5]

Click to learn more about the long-term complications of AHP that add to disease burden

Click for abbreviations and references

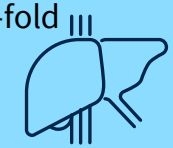
*EXPLORE-A (N=112) included patients who had 3 attacks or more or were receiving prophylactic treatment.[3]

Delayed Diagnosis Can Lead to the Development of Serious Long-Term Complications Which Add to the Disease Burden Experienced by Patients with AHP

Long-term complications of AHP

Primary liver cancer

- Hepatoma should be considered if a patient develops abdominal pain after long-term remission[19]
- A Norwegian registry cohort study found the risk of **primary liver cancer** was 108-fold higher over the lifetime of patients with AHP (n=251) versus controls[26]



Chronic sustained hypertension

- **Hypertension is more prevalent** among patients with AIP compared with the general population[19]

Chronic kidney disease

- ALA and PBG have potential nephrotoxic effects, leading to oxidative stress and tissue injury[27]
- **Repeated AHP attacks lead to acute kidney injury[27]**

Neuronal damage

- Both experimental and clinical data demonstrated that ALA accumulation has highly neurotoxic effects, responsible for **neuropathy and axonal degeneration** via multiple proposed mechanisms[28,29]

Click for abbreviations and references

Practical Guidance for Measuring PBG and ALA

Substantial elevation of urine PBG and ALA is a distinctive biochemical feature of AHP, and therefore, a key diagnostic tool[4]

Ordering tests

- **Porphyrin tests do not include ALA and PBG**, as they are porphyrin precursors[4]
- It is key to request the correct test to ensure informative results are obtained[1,7]

Analyzing results

- **Substantial PBG elevation has a high degree of specificity and sensitivity for AIP, VP, or HCP** because an elevation many times above normal does not occur in any other medical condition[1]
  - ALA elevation is indicative of the ultra-rare AHP subtype ADP, in which PBG levels are normal or only slightly elevated[1]
- ALA and PBG excretion should be **normalized to creatinine** to adjust for differences in the degree of urinary concentration[4]
  - The ULN for ALA and PBG are 1.47 and 0.137 mmol/mol Cr, respectively[30]

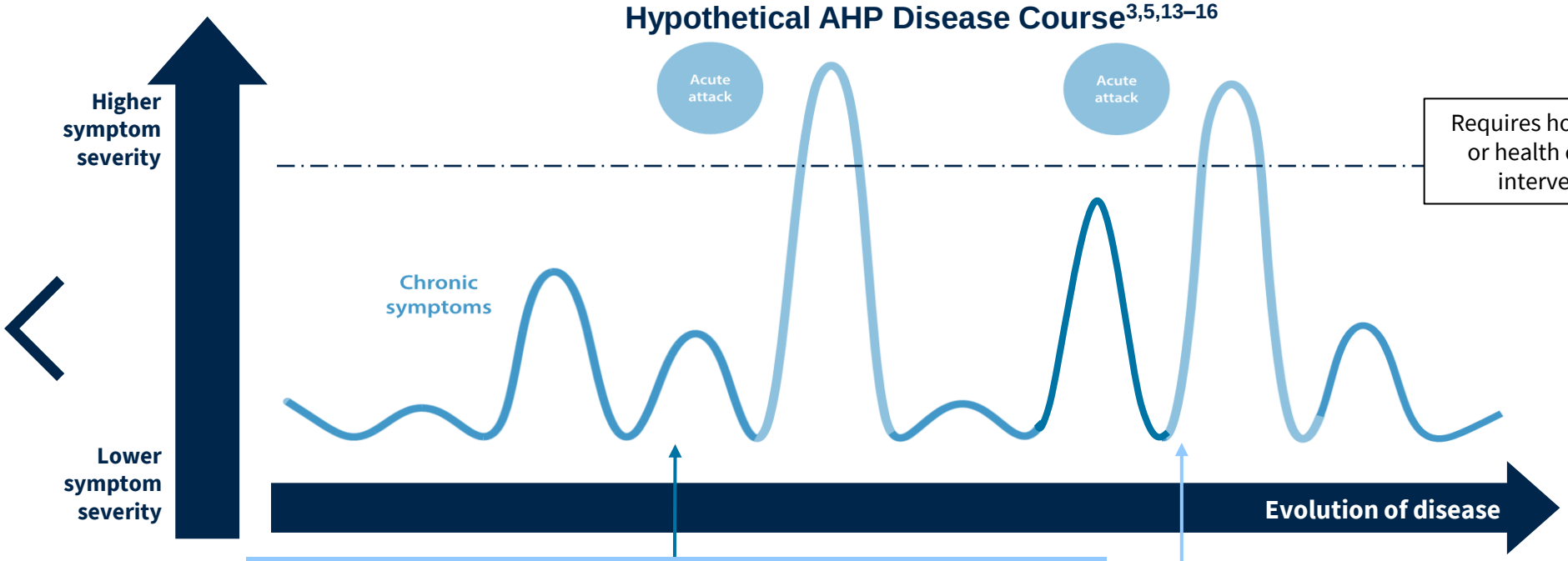
Considerations

- Both ALA and PBG can be measured with high sensitivity and specificity, but both often require large reference laboratories and **results can take 1–2 weeks to be reported[4]**
  - Despite challenges, it is important to test for ALA and PBG as biochemical testing is required for AHP diagnosis[4]

Click for abbreviations and references

ALA and PBG Levels Can Vary Depending on AHP Type and Timing of Measurement, Therefore Repeat Testing May be Required for a Diagnosis

Hypothetical AHP Disease Course[3,5,13–16]



Testing in between acute attacks[4]

- In patients with recurrent acute attacks, urine ALA and PBG are typically elevated even at baseline between attacks
  - Studies of patients with AIP found that ALA and PBG can remain elevated in urine for months to years after an acute attack*
- If testing is performed in patients with sporadic AIP when they are asymptomatic , they can have normal urine ALA and PBG values. Confirmation testing may require repeat testing during an acute attack

Testing during an acute attack[4]

For most patients with AHP, testing for urine ALA, PBG, and Cr is most useful during an acute attack

*ALA and PBG levels can fall quickly after an acute attack in patients with HCP or VP.[4]

Click for abbreviations and references

Genetic Counselling is Recommended for Patients and Carriers[4]

Genetic testing of the 4 genes *ALAD*, *HMBS*, *CPOX*, and *PPOX* leads to ADP, AIP, HCP, and VP diagnosis, respectively

Although genetic testing can confirm a diagnosis, it is **not recommended for initial screening**

- This is because the **estimated phenotypic penetrance** of symptomatic disease is **approximately 1%** of AIP gene carriers
- This increases to **>20%** in **families of symptomatic patients**

Once the familial pathogenic variant has been identified in the patient, **first-degree family members should be screened** to identify at-risk patients. Those who are mutation carriers should receive genetic counselling

Click for abbreviations and references

Abbreviations and References

A, acute; ADP, ALA dehydratase-deficient porphyria; AHP, acute hepatic porphyria; ALAD, aminolevulinate dehydratase; ALAS1, ALA synthase 1; AIP, acute intermittent porphyria; ALA, δ-aminolevulinic acid; C, chronic; Cr, creatinine; CoA, coenzyme A; CPOX, coproporphyrinogen oxidase; CYP450, cytochrome P450, HCP, hereditary coproporphyria; HMBS, hydroxymethylbilane synthase; PBG, porphobilinogen; PPOX, protoporphyrinogen oxidase; ULN, upper limit of normal; VP, variegate porphyria.

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