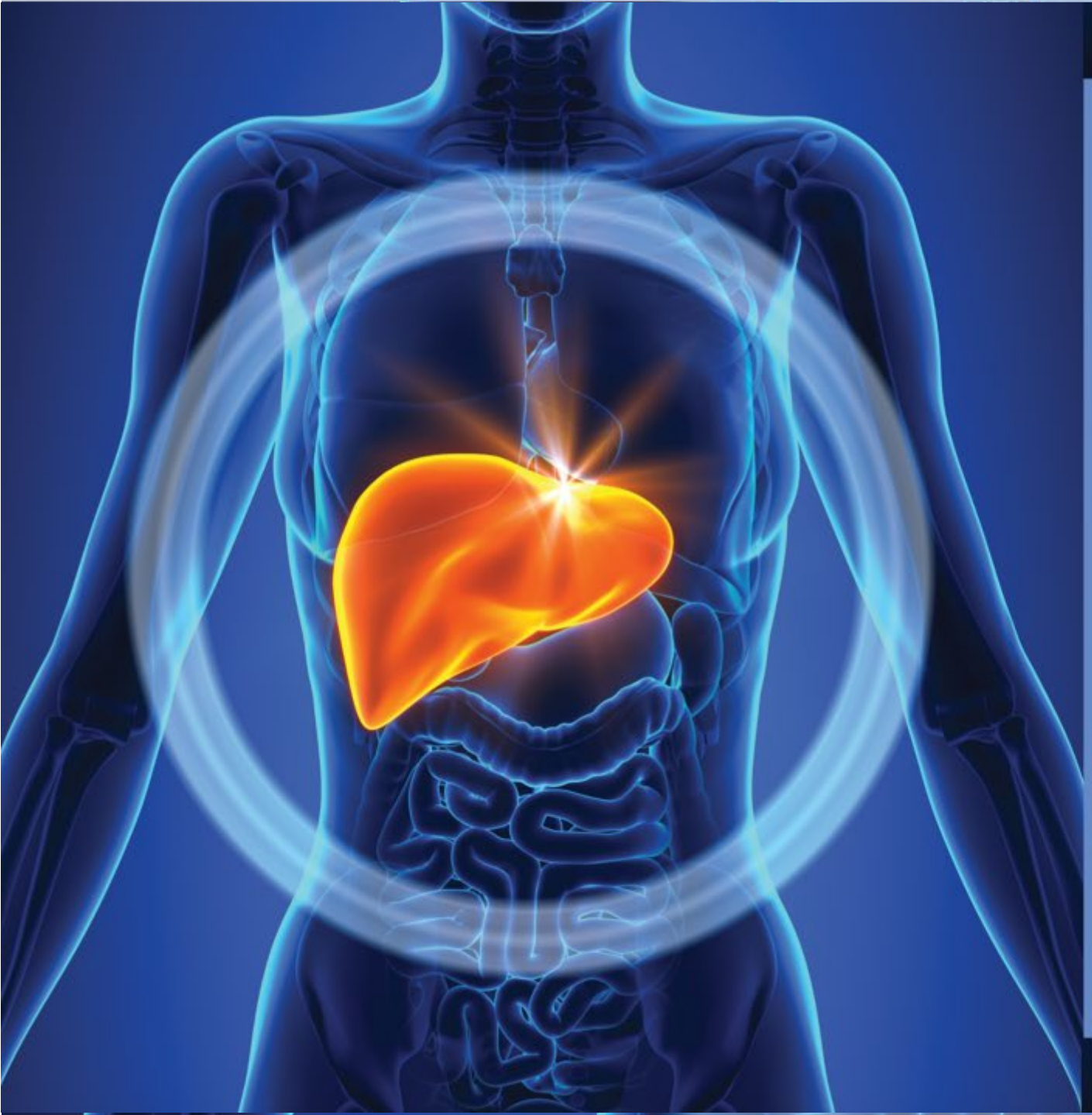

A Deeper Dive into Unexplained Abdominal Pain:

Facilitating the Diagnosis and Management of Acute Hepatic Porphyria in the Gastroenterology Setting

Faculty

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This program is jointly provided by AKH Inc., Advancing Knowledge in Healthcare and Catalyst Medical Education, LLC

PROGRAM OVERVIEW

Acute hepatic porphyria (AHP) is a group of rare inherited diseases with variable, non-specific, and dynamic symptoms and associated with an average diagnostic delay of 15 years. During that time, patients experience hallucinations, dreadful pain, seizures, and frequent hospitalizations. This activity will educate gastroenterologists and other healthcare providers on the hallmark signs of AHP, strategies for differential diagnosis, and current management options for improving patient outcomes.

TARGET AUDIENCE

This initiative is intended for gastroenterologists, physicians, nurses, physician assistants and other healthcare professionals assessing patients in the gastroenterology setting.

COMMERCIAL SUPPORT

This activity is supported by an educational grant from Alnylam Pharmaceuticals, Inc.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- **EXPLAIN** the etiology and pathophysiology of severe abdominal pain related to AHP
- **IDENTIFY** signs and symptoms suggestive of AHP among individuals presenting with severe abdominal pain
- **DEFINE** strategies to differentially diagnose AHP from other gastrointestinal (GI) and non-GI conditions
- **ASSESS** treatment and management options for AHP, including disease-specific therapies
- **PROPOSE** interdisciplinary strategies to individualize clinical management of AHP in the gastroenterology setting

Agenda

- Introduction
- **Recognizing Signs and Symptoms of AHP in Patients**
- **Strategies for Screening AHP and Reaching a Differential Diagnosis**
- **Improving AHP Patient Care: Focusing on Disease-Specific Therapy**
- Question and Answer

CRITERIA FOR SUCCESS

Certificates of completion will be awarded based on the participant's attendance and submission of the activity evaluation/claim credit form. You must participate in the entire activity to receive credit. There is no fee to participate in this activity. If you have questions about this activity, please contact AKH Inc. at tbrignoni@akhcme.com.

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In support of improving patient care, this activity has been planned and implemented by AKH Inc., Advancing Knowledge in Healthcare and Catalyst Medical Education, LLC. AKH Inc., Advancing Knowledge in Healthcare is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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1.5 ANCC contact hours

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This course is designed solely to provide the healthcare professional with information to assist in his/her practice and professional development and is not to be considered a diagnostic tool to replace professional advice or treatment. The course serves as a general guide to the healthcare professional, and therefore, cannot be considered as giving legal, nursing, medical, or other professional advice in specific cases. AKH Inc. specifically disclaim responsibility for any adverse consequences resulting directly or indirectly from information in the course, for undetected error, or through participant's misunderstanding of the content.

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Disclosures

Faculty

Karl E. Anderson, MD, FACP (Chairperson), has disclosed the following relevant financial relationships: Consultant and Researcher: Alnylam Pharmaceuticals Mitsubishi Tanabe Pharma USA, Recordati Rare Diseases

D. Montgomery Bissell, MD, has no financial relationships to disclose.

Herbert Lloyd Bonkovsky, MD, has disclosed the following relevant financial relationships: Consultant: Disc Medicine, Protagonist Therapeutics, Recordati Rare Chemicals; Researcher (Awarded to Wake Forest): Alnylam Pharma, Mitsubishi-Tanabe

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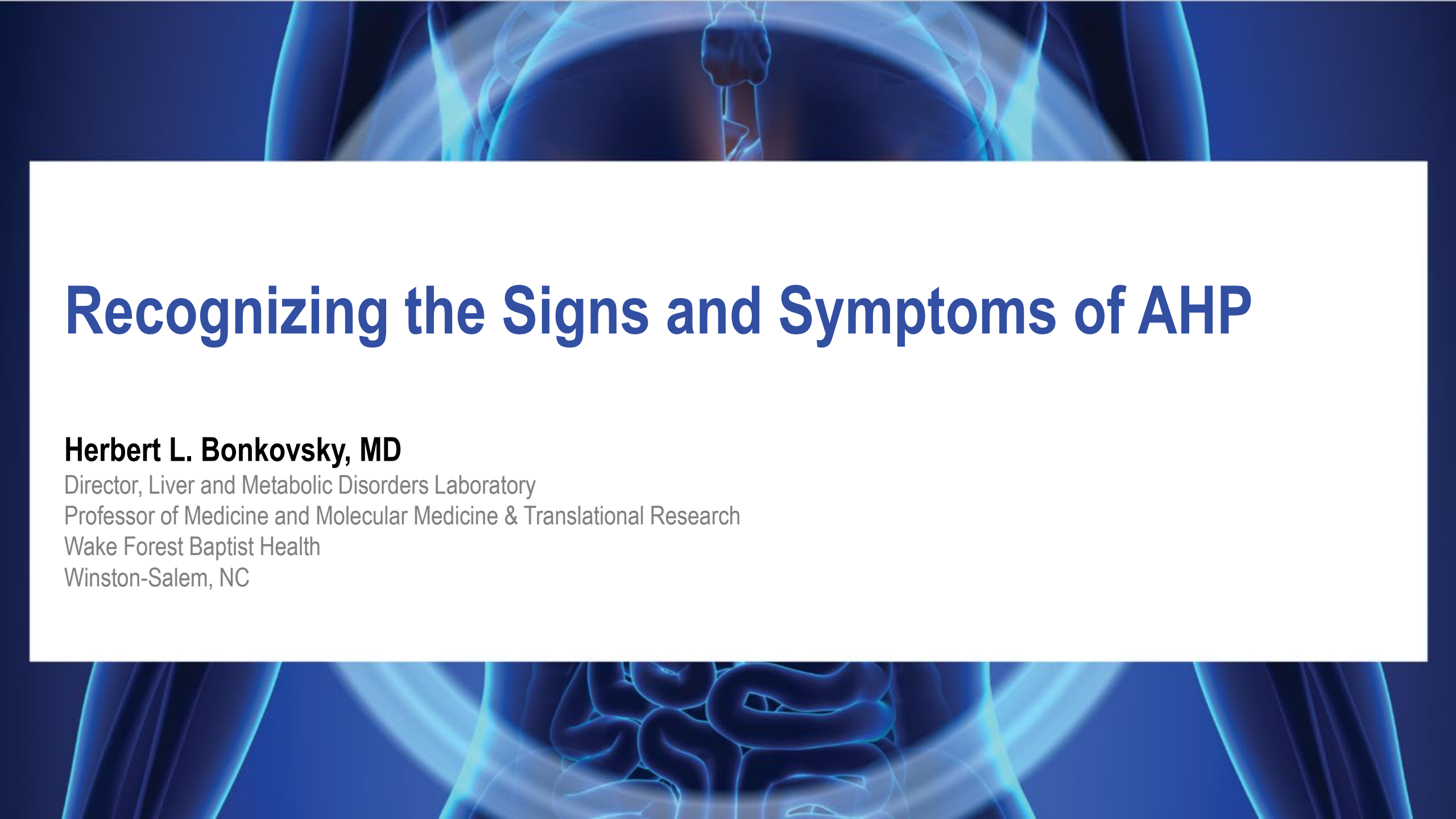

Recognizing the Signs and Symptoms of AHP

Herbert L. Bonkovsky, MD
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Winston-Salem, NC

Porphyrias: Definition

- Disorders of normal porphyrin and heme synthesis
- Mostly inherited, but drugs, nutrition, alcohol, other genetic variations have effects
- Main clinical features: acute neurovisceral attacks or cutaneous photosensitivity
- Symptoms due to effects of ALA or porphyrins
- Most common are AIP, PCT, EPP

AIP: acute intermittent porphyria; ALA: 5-aminolevulinic acid; EPP: erythropoietic protoporphyria; PCT: porphyria cutanea tarda.

Bonkovsky HL, et al. *Compr Physiol*. 2013;3:365-401. Bissell DM, et al. *N Engl J Med*. 2017;377:862-872. Bonkovsky HL, et al. *Mol Genet Metab*. 2019;128:213-218.

Classification of Porphyrias According to Main Site of Overproduction

- Hepatic porphyrias
  - —Acute or inducible porphyrias: 4 types
  - —Chronic hepatic porphyrias
    - PCT
    - HEP
- Erythropoietic porphyrias
  - —CEP
  - —EPP

CEP: congenital erythropoietic porphyria; EPP: erythropoietic protoporphyria; HEP: hepatoerythropoietic porphyria; PCT: porphyria cutanea tarda.

Bonkovsky HL, et al. *Compr Physiol*. 2013;3:365-401. Bissell DM, et al. *N Engl J Med*. 2017;377:862-872. Bonkovsky HL, et al. *Mol Genet Metab*. 2019;128:213-218.

Classification of Porphyrias According to Main Clinical Features

- Acute porphyrias: neurological features
  - AIP
  - HCP*
  - VP*
  - Porphyria due to severe ALA-D (ADP) deficiency
- Cutaneous porphyrias
  - PCT
  - EPP/XLP
  - CEP
  - HEP

*May also produce cutaneous lesions.
ADP: 5-aminolevulinic acid dehydratase deficient porphyria; AIP: acute intermittent porphyria; ALA-D: 5-aminolevulinic acid dehydratase; CEP: congenital erythropoietic porphyria; EPP: erythropoietic protoporphyria; HCP: hereditary coproporphyria; HEP: hepatoerythropoietic porphyria; PCT: porphyria cutanea tarda; VP: variegate porphyria; XLP: X-linked protoporphyria.

Question

What is the most useful screening test for making a rapid diagnosis of acute hepatic porphyria?

A. Urinary porphyrin screen
B. Urinary porphobilinogen and creatinine
C. Stool porphyrins
D. Plasma porphyrin concentration

Question

What is the most useful screening test for making a rapid diagnosis of acute hepatic porphyria?

A. Urinary porphyrin screen
B. Urinary porphobilinogen and creatinine
C. Stool porphyrins
D. Plasma porphyrin concentration

Correct answer = B. Urinary porphobilinogen and creatinine

Case: 18-Year-Old Woman

- Medical History: takes oral contraceptives, is generally healthy
  - CC: severe abdominal pain, goes to ED
- Vitals
  - BP 150/96 mm Hg
  - PR 110 bpm
  - Temperature 99.5 °F
- Physical exam
  - Severe pain (rated 10 of 10), mainly in the lower abdomen
  - Abdomen is soft
  - Bowel sounds are absent
- CT of abdomen shows retained stool in colon, no gallstones, normal appendix
- Seen in consultation by GI and General Surgery
  - Both specialists determined that no acute surgical problem was present
- Patient is admitted for “observation” and treated with IV fluids and narcotic analgesics
  - Pain gradually improves over 24 hours
  - No clear diagnosis

BP: blood pressure; CC: chief concern; CT: computed tomography; ED: emergency department; GI: gastroenterology; IV: intravenous; PR: pulse rate.

Case: 18-Year-Old Woman (cont)

- Patient does well for 6 months
- Goes to a fraternity party at college
  - Drinks to excess with poor nutritional intake
- Again, develops severe abdominal pain, requiring a visit to the ED
- Presentation
  - Mild fever
  - Elevated WBC count
  - Normal abdominal CT scan
- Undergoes appendectomy despite the lack of localizing signs to RLQ; appendix shows “mild chronic inflammation”
- Patient receives IV dextrose and analgesics
  - Improves and is discharged after 3 days

CT: computed tomography; ED: emergency department; IV: intravenous; RLQ: right lower quadrant; WBC: white blood cell.

Case: 18-Year-Old Woman (cont)

- Patient experiences further acute attacks of abdominal pain with tachycardia and hypertension
- Repeat abdominal US and CT scans show no abnormalities except for retained stool in the colon
- Patient notes dark reddish-brown urine
- An astute medical student considers a diagnosis of AIP and obtains urine for PBG and creatinine measurement
- Patient is again treated with analgesics, antinausea medications, and IV fluids
- After 10 days, results are received: PBG 60 mg/g creatinine

AIP: acute intermittent porphyria; CT: computerized tomography; IV: intravenous; PBG: porphobilinogen; US: ultrasound.

Question

True or false? Attacks of acute hepatic porphyria occur only in white women.

A. True
B. False

Question

True or false? Attacks of acute hepatic porphyria occur only in white women.

A. True
B. False

Correct answer = B. False

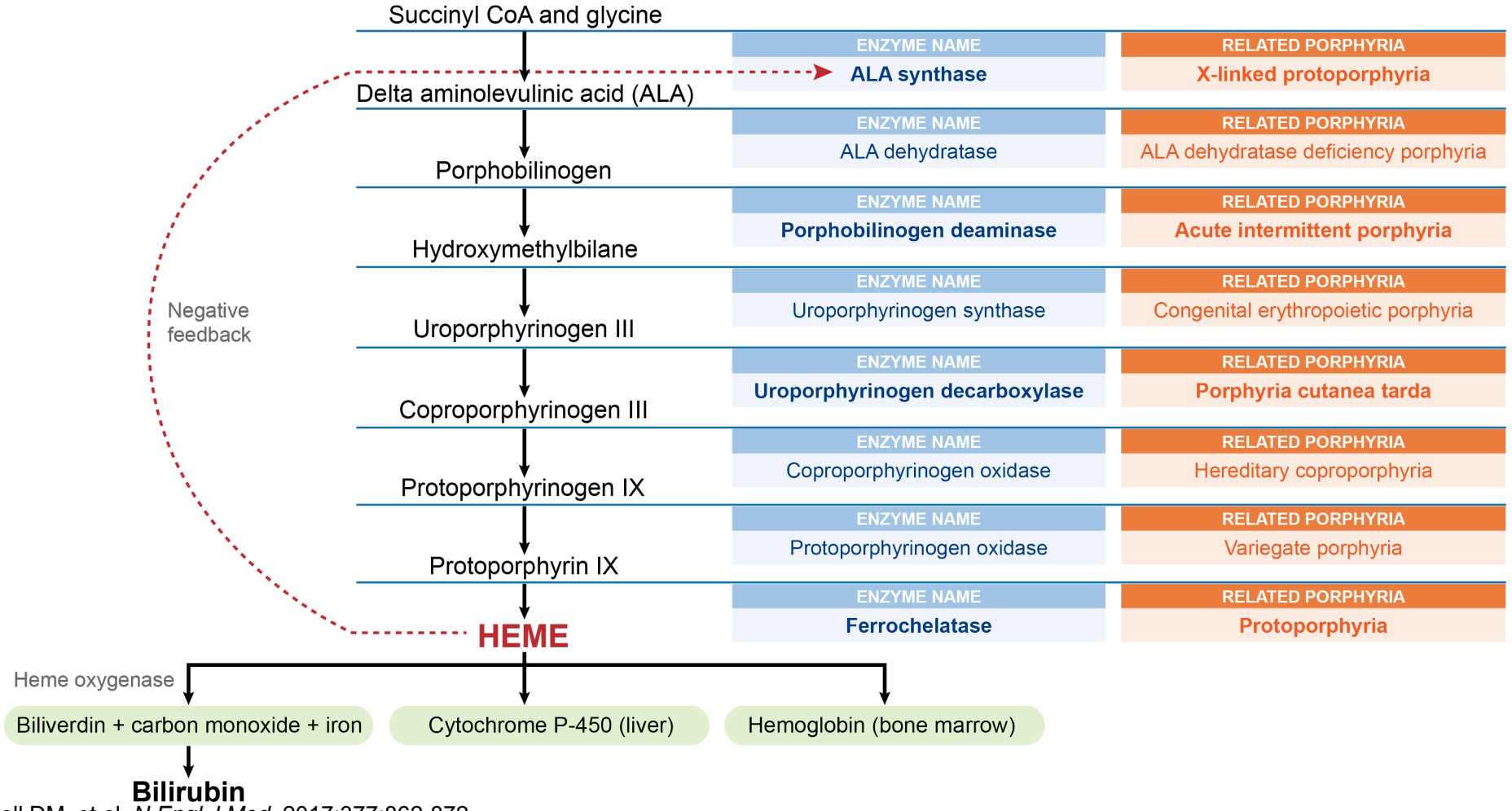
Overview of Mammalian Heme Synthesis

- Heme is made in nearly all cells in the body
- Most heme synthesized each day is made in either:
  - Developing red blood cells (~80%)
  - Hepatocytes (~15%)
- Erythroid heme synthesis always occurs at a high level
  - Acute blood loss, hemolysis, etc. may lead to further and major increases
- Hepatic heme synthesis varies widely
  - Depends on changing metabolic requirements, especially CYPs
- For both erythroid and hepatic heme synthesis
  - Rate-controlling step = 1st step
  - Catalyzed by ALA synthase

ALA: 5-aminolevulinic acid; CYP: cytochrome P.

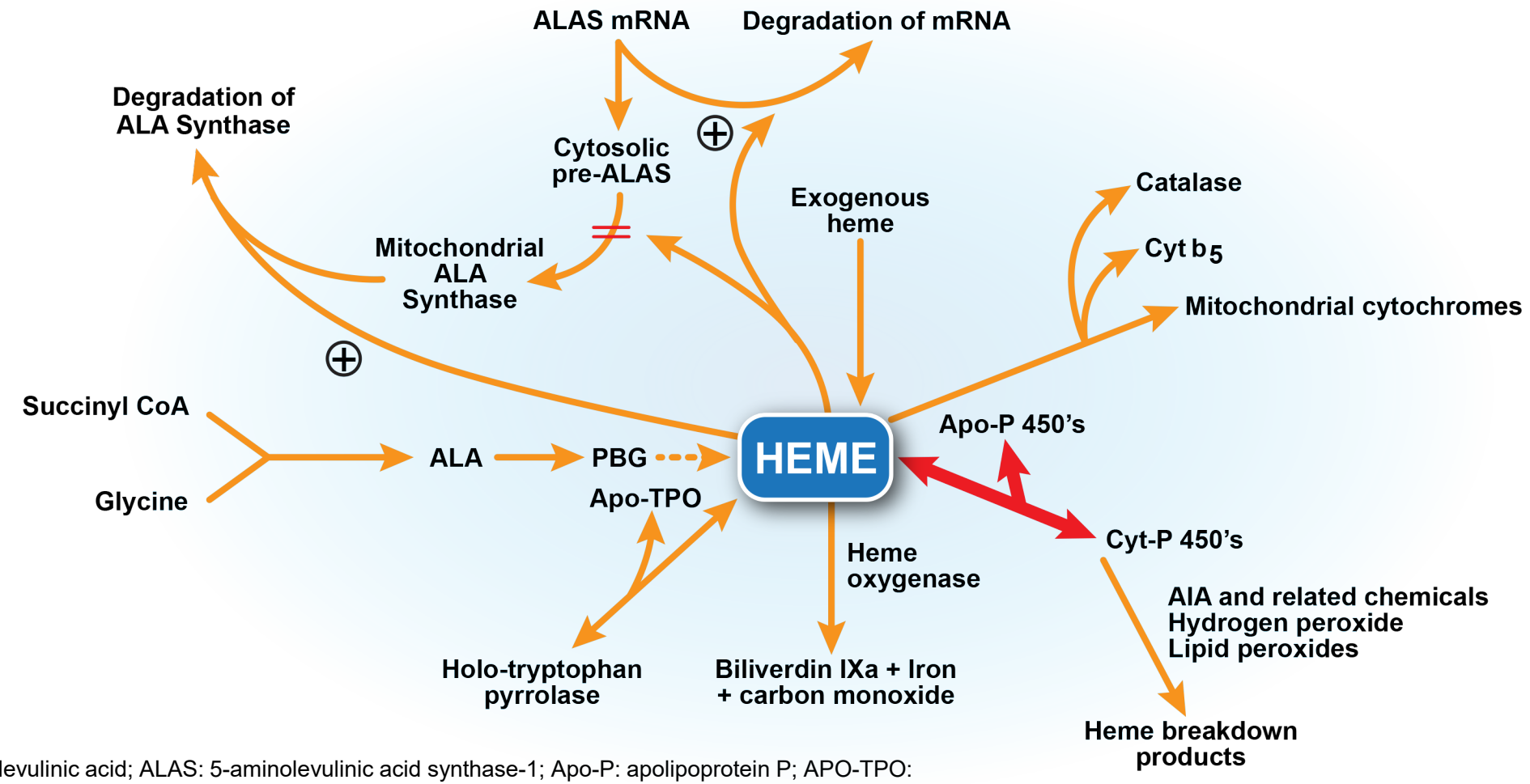
Ferreira GC. Heme synthesis. In: Lennarz WJ, Lane MD, ed. *Encyclopedia of Biological Chemistry*. 2nd ed. Academic Press; 2013:539-542.

Pathway of Heme Metabolism and Types of Porphyria



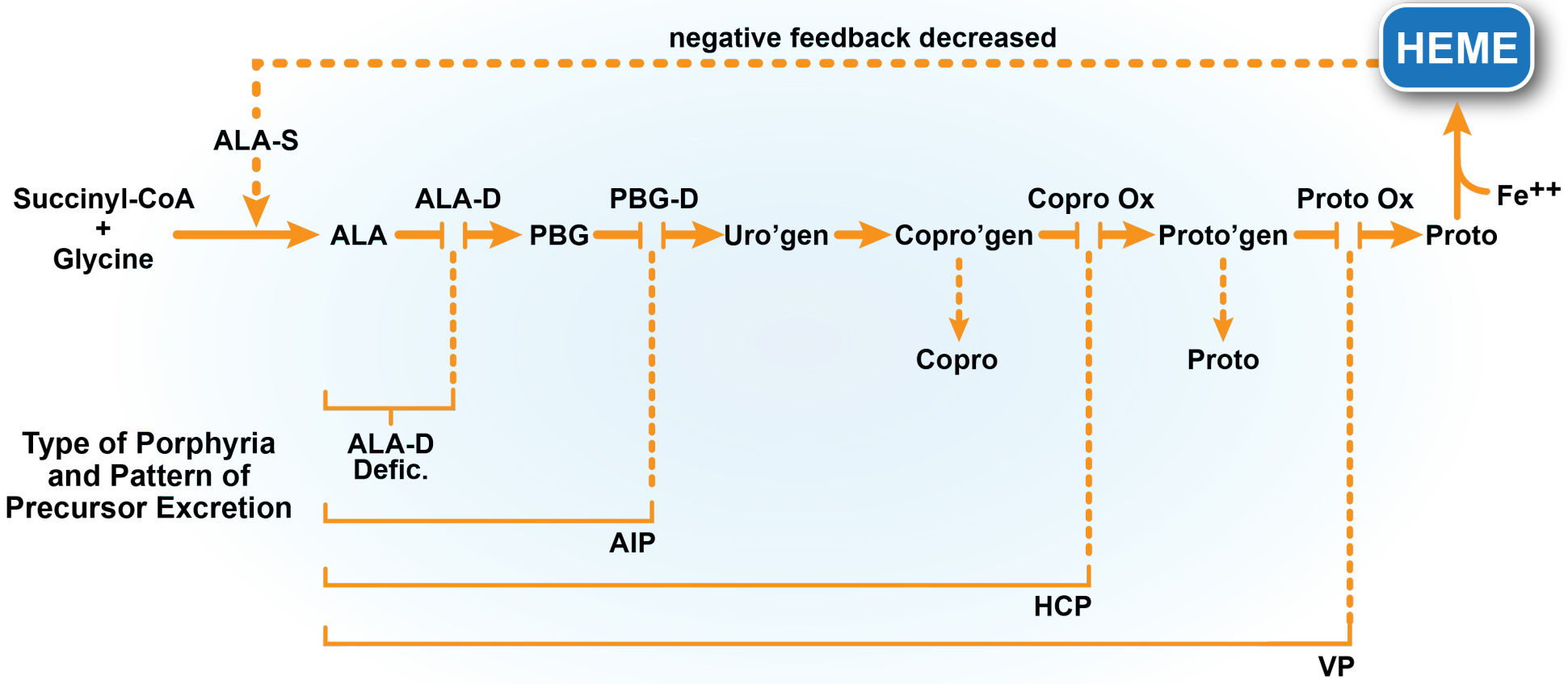
Bissell DM, et al. *N Engl J Med*. 2017;377:862-872.

Regulation of Hepatic Heme Metabolism



ALA: 5-aminolevulinic acid; ALAS: 5-aminolevulinic acid synthase-1; Apo-P: apolipoprotein P; APO-TPO: apolipoprotein tryptophan; Cyt b_5: cytochrome b_5: Cyt P450: cytochrome P450; PBG: porphobilinogen.
Courtesy of H.L. Bonkovsky, MD.

Metabolic Defects and Patterns of Precursor Excretion in Acute Porphyrias



AIP: acute intermittent porphyria; ALA: 5-aminolevulinic acid; ALA-D: 5-aminolevulinic acid dehydratase; ALAS: 5-aminolevulinic acid synthase-1; CoA: coenzyme A; Fe^{++}: iron; HCP: hereditary coproporphyria; Ox: oxidase; PBG: porphobilinogen; PBG-D: porphobilinogen deaminase; VP: variegate porphyria.

Courtesy of H.L. Bonkovsky, MD.

Selected Features of the 4 Acute Porphyrias, Genes, Enzymes

Type	Inheritance	Deficient Enzyme	Subcellular Location	Enzyme Activity (% NI)	Known Mutations (no.)	Gene Locus	OMIM No.
AIP	Autosomal dominant	PBG-D (HMBS)	Cytosol	~50	~400	11q23.3	176000
HCP	Autosomal dominant	Coproporphyrinogen oxidase	Mitochondria	~50	~50	3q12	121300
VP	Autosomal dominant	Protoporphyrinogen oxidase	Mitochondria	~50	~130	1q22	176200
ALA-D deficiency	Autosomal recessive	ALA-D (PBG synthase)	Cytosol	~5	~10	9q34	125270

AIP: acute intermittent porphyria; ALA-D: 5-aminolevulinic acid dehydratase; HCP: hereditary coproporphyria; HMBS: hydroxymethylbilane synthase; NI: normal; PBG: porphobilinogen; PBGD: porphobilinogen deaminase; VP: variegate porphyria.

Courtesy of H.L. Bonkovsky, MD.

Acute Intermittent Porphyria: Estimated Prevalence of Disease

- Depends on country and region: founder effects
  - —Sweden 8-10 per 100,000
  - —Finland 2-3 per 100,000
  - —UK & Western Europe 2-5 per 100,000
  - —USA 2-5 per 100,000
- Prevalence of genetic defects is much higher: ~65 per 100,000
  - —Implies low penetrance

Courtesy of HL Bonkovsky, MD.

Acute Porphyrias: Main Clinical Features

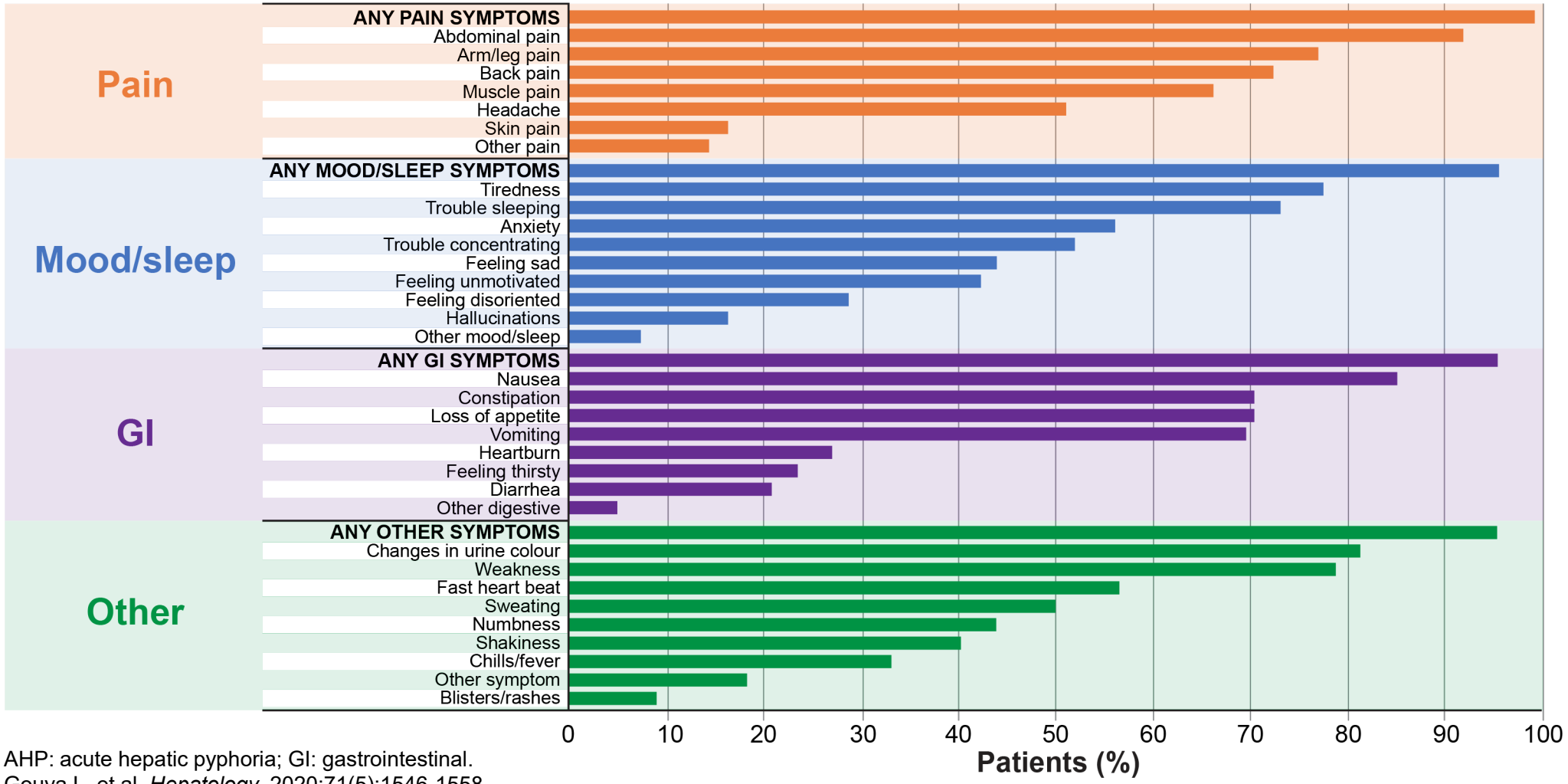
- Overlapping clinical syndromes due to neuron dysfunction or death
  - Acute attacks: pain crises, autonomic disease
  - Peripheral sensory-motor neuropathy
  - Progression to truncal, CN, global CNS dysfunction
- Subacute or chronic pain and paresthesias
- Seizures (occur in 20% of patients)

CN: cranial nerve; CNS: central nervous system.

Bissell DM, et al. *N Engl J Med*. 2017;377:862-872. Bonkovsky HL, et al. *Mol Genet Metab*. 2019;128:213-218.

Clinical Features of Acute AHP

Select Clinical Features of Patients With AHP Who Have Acute Attacks (n = 112)

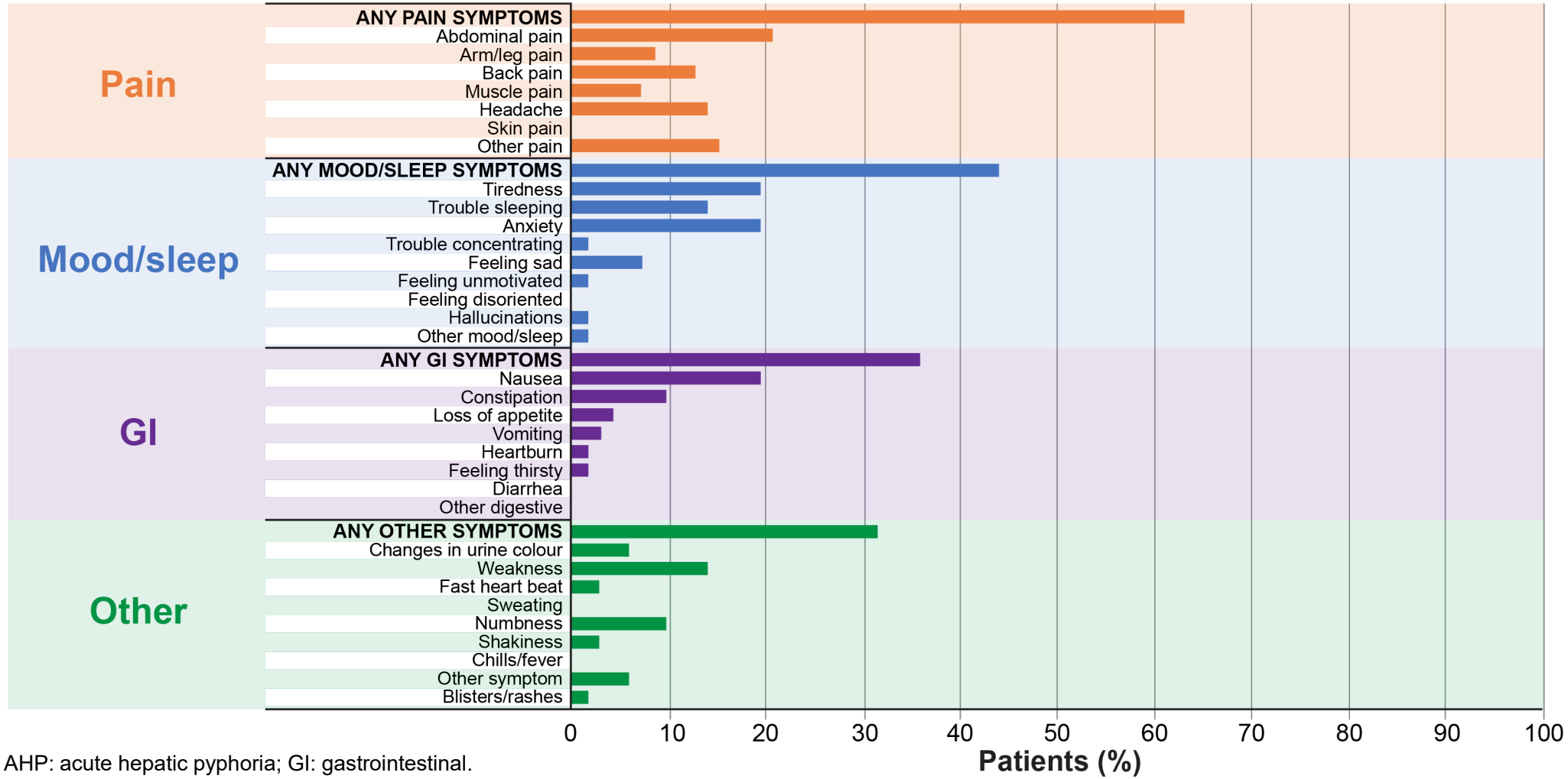


AHP: acute hepatic pyphoria; GI: gastrointestinal.

Gouya L, et al. *Hepatology*. 2020;71(5):1546-1558.

Clinical Features of Chronic AHP

Select Clinical Features of Patients With AHP Who Have Chronic Symptoms (n = 73/112)



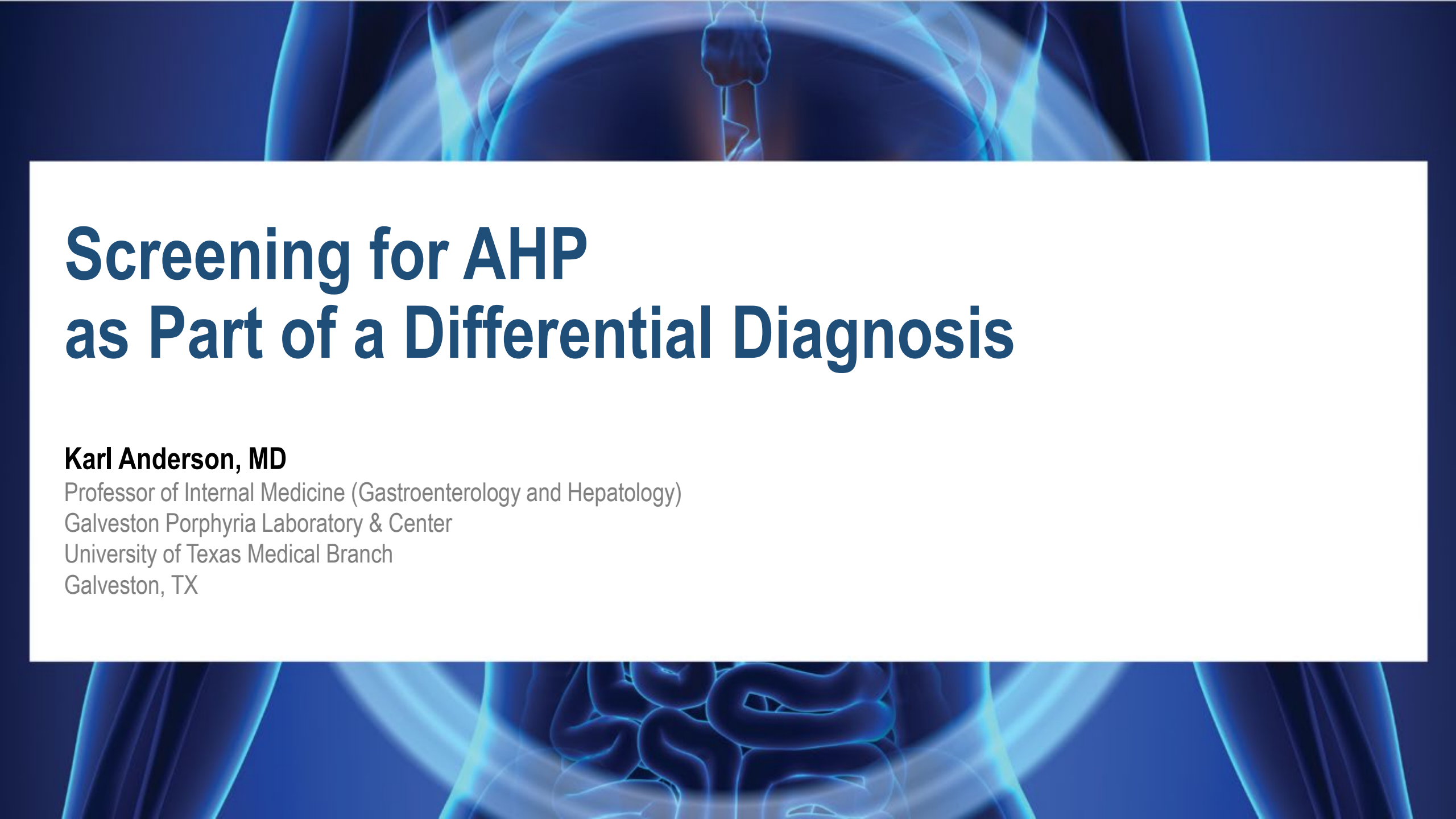
AHP: acute hepatic pyphoria; GI: gastrointestinal.

Gouya L, et al. *Hepatology*. 2020;71(5):1546-1558.

Conclusions

- Porphyrias are caused by defects in the heme biosynthetic pathway
- Acute hepatic porphyrias are primarily autosomal dominant
  - Men and women of any ethnicity can be affected
  - Attacks do, however, occur more frequently in women
- Symptoms are primarily due to injury to the nervous system
- Key clinical features that are suggestive of AHP include:
  - Acute pain crises with subtle neurological signs
  - Poor response to analgesics, including opioids
  - GI symptoms with normal abdominal findings
  - Tachycardia
  - Elevated SBP
- Urinary PBG/creatinine is the most useful test for screening patients

GI: gastrointestinal; PBG: porphobilinogen; SBP: systolic blood pressure.



Screening for AHP as Part of a Differential Diagnosis

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Acute Hepatic Porphyria (AHP)

- Four rare inherited diseases with primarily neurological symptoms
  - AIP is the most common AHP
  - VP and HCP may cause chronic blistering photosensitivity
- Symptoms are nonspecific even when severe and life-threatening
- Diagnostic testing is sensitive, specific, and widely available
- AHP is seldom part of a differential diagnosis and laboratory testing, so delays in diagnosis are common
- Treatments are available that hasten recovery and may be life-saving
  - They are most beneficial if applied early, before extensive neurological damage occurs

AIP: acute intermittent porphyria; HCP: hereditary coproporphyria; VP: variegate porphyria.

Bonkovsky HL, et al. *Compr Physiol*. 2013;3:365-401. Bissell DM, et al. *N Engl J Med*. 2017;377:862-872.

AHP Mimics Other More Common Conditions

- Abdominal pain is the most common symptom
  - Usually acute, often recurrent, and sometimes chronic
  - Neuropathic and noninflammatory, so physical findings are often minimal
  - Often accompanied by other GI manifestations such as ileus, distension, nausea and vomiting, constipation, and urinary retention
  - Pain is usually severe, requiring opioids
- Accompanied often by:
  - Tachycardia and hypertension
  - Pain in the back, chest, and extremities
  - Agitation, restlessness, hallucinations, and seizures (sometimes with hyponatremia)
  - Motor neuropathy and paresis, which usually occur after a few days without treatment

AHP: acute hepatic porphyria; GI: gastrointestinal.
Bissell DM, et al. *N Engl J Med*. 2017;377:862-872.

AHP Presentation Overlaps With Other Conditions

Such overlap can cause:

- *Abdominal or pelvic pain*: appendicitis, diverticulitis, endometriosis, ectopic pregnancy, pelvic inflammatory disease, cholecystitis/lithiasis, pancreatitis, peptic ulcer disease, inflammatory bowel disease, and many other conditions
- *Motor neuropathy*: especially Guillain-Barré syndrome
- *Psychiatric symptoms*: especially if acute and accompanied by abdominopelvic symptoms or motor weakness

AHP: acute hepatic porphyria.

Anderson KE. *Mol Genet Metab*. 2019;128:219-227. Bonkovsky HL, et al. *Mol Genet Metab*. 2019;128:213-218.

When Should AHP Be Considered and Tested for?

- Low index of suspicion
  - —Unexplained acute abdominal or pelvic pain after an initial workup (eg, H&P, WBC count, lipase, LFTs, pregnancy test, and imaging) does not reveal a cause
  - —Motor neuropathy resembling that in GBS
- High index of suspicion
  - —If diagnostic "pattern recognition" suggests a systemic disorder such as AHP
    - For example, a woman with abdominopelvic symptoms or motor weakness accompanied by agitation, hallucinations, seizures, hyponatremia, ileus, urinary retention, etc.

AHP: acute hepatic porphyria; GBS: Guillain-Barré syndrome; H&P: history and physical; LFT: liver function test; WBC: white blood cell.
Bonkovsky HL, et al. *Mol Genet Metab*. 2019;128:213-218.

Preferred Laboratory Testing for AHP When Symptoms Are Present

- Apply only first-line (screening) tests that are sensitive and inexpensive, and that can be done only once in many patients with consistent symptoms, particularly abdominal pain
  - **Spot urine test for PBG and total porphyrins**
    - Initial results can be expressed per liter, but final results should be normalized to creatinine
    - If results are negative but some suspicion of porphyria remains:
      - Repeat first-line testing at a later date, rather than apply second-line testing

AHP: acute hepatic porphyria; PBG: porphobilinogen.
Anderson KE. *Mol Genet Metab.* 2019;128:219-227.

Preferred Laboratory Testing for AHP When Symptoms Are Present (cont)

- Second-line tests (only when first-line testing is positive): multiple tests that are done infrequently, so the higher cost is justified
  - **Spot urine test for ALA, PBG, and porphyrins (fractionated if elevated), plasma porphyrins (including fluorescence scan), fecal porphyrins (fractionated if elevated)**
  - Possible outcomes of second-line testing:
    - Elevated urine porphyrin represents nonspecific porphyrinuria due to another medical condition, *or*
    - Result establishes a biochemical diagnosis of AIP, VP, HCP, or ADP
- DNA testing (after the type of AHP has been established biochemically)
  - Confirms a diagnosis
  - Enables screening of family members

ADP: ALA dehydratase porphyria; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALA: δ-aminolevulinic acid; HCP: hereditary coproporphyria; PBG: porphobilinogen; VP: variegate porphyria.

Anderson KE. *Mol Genet Metab*. 2019;128:219-227.

Second-Line Testing: Fecal Porphyrins

Important for differentiating AIP, HCP, and VP

Acute Porphyria	Total Fecal Porphyrins	Pattern of Individual Porphyrins
ALA dehydratase porphyria	Normal or slightly elevated	Normal
AIP	Normal or slightly elevated	Normal
HCP	Markedly elevated	Mostly coproporphyrin III
VP	Markedly elevated	Mostly coproporphyrin III and protoporphyrin IX

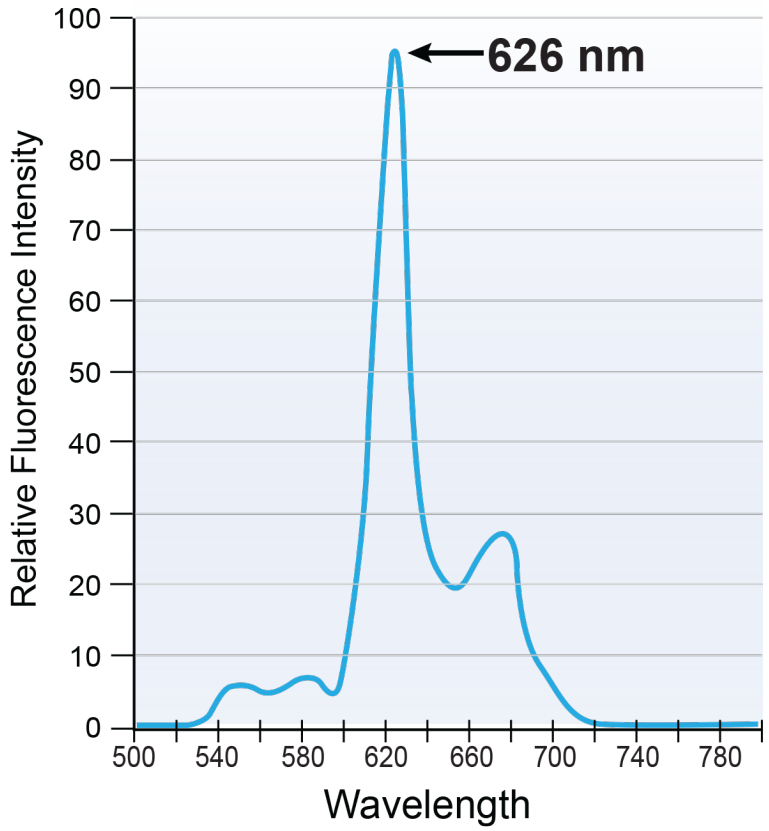
AIP: acute intermittent porphyria; HCP: hereditary coproporphyria; VP: variegate porphyria.

Pischik E, et al. *Appl Clin Genet*. 2015;8:201-214.

Second-Line Testing: Plasma Porphyrins

Fluorescence scanning of diluted plasma at a neutral pH is especially important for identifying VP

Acute Porphyria	Plasma Porphyrins	Peak Wavelength at Neutral pH
ALA dehydratase porphyria	Normal or slightly elevated	~619 nm
AIP	Normal or slightly elevated	~619 nm
HCP	Normal or slightly elevated	~619 nm
VP	Usually elevated	~626 nm



AIP: acute intermittent porphyria; HCP: hereditary coproporphyria; VP: variegate porphyria.

Poh-Fitzpatrick MB. *Arch Dermatol*. 1980;116:543-547. Zaider E, et al. *Clin Dermatol*. 1998;16(2):277-93.

Preferred Laboratory Testing for AHP When Symptoms Are Absent

- For example:
  - Patient previously had symptoms suggesting AHP
  - Patient is an asymptomatic family member of a patient with known or suspected AHP
- Because first-line testing may be negative in the absence of symptoms, options are:
  - Second-line testing, which is more sensitive than first-line testing in this setting, *or*
  - DNA testing, especially if a familial mutation has been previously identified in a relative

AHP: acute hepatic porphyria.

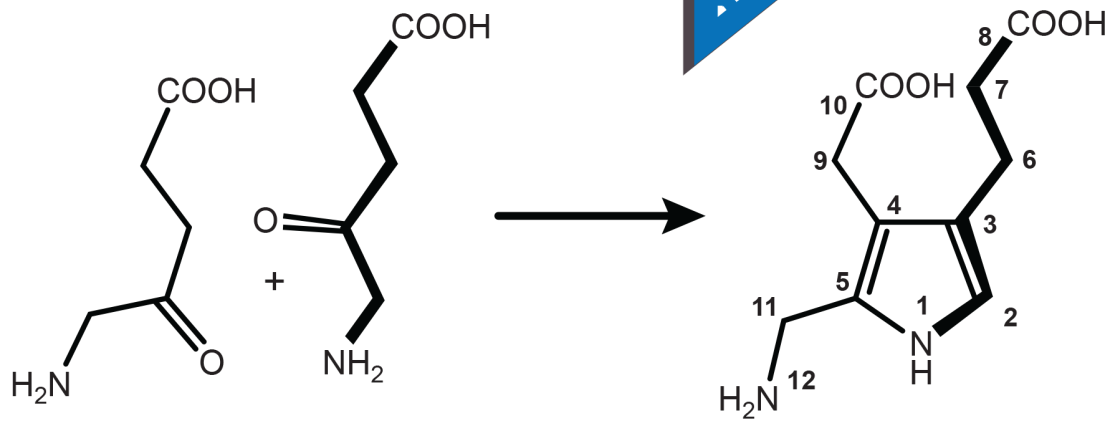
Anderson KE. *Mol Genet Metab*. 2019;128:219-227.

Porphyrin Precursors and Porphyrins

- PBG is a pyrrole, not a porphyrin, and ALA is an amino acid
- Given their diagnostic importance in first- and second-line testing, it is important to order urine PBG and porphyrins specifically
- Ordering a “porphyrin screen” or “porphyrin panel” is vague and not appropriate, and PBG may not be measured

Remember:

Pyrrole, *not a porphyrin*



δ-Aminolevulinic acid

Porphobilinogen

ALA: 5-aminolevulinic acid; PBG: porphobilinogen.

Anderson KE. *Mol Genet Metab*. 2019;128(3):219-227.

DNA Testing for AHP

- Identifies a pathogenic mutation that is consistent with biochemical findings
  - —Is now considered standard of care
  - —Confirms a diagnosis
  - —Enables family members to be screened accurately by targeted mutation analysis
- Caveats with DNA testing
  - —Rare “cryptic” mutations may be difficult to identify and can be missed
  - —An identified pathogenic mutation may not explain symptoms
    - Because most individuals with mutations are asymptomatic
    - Therefore, biochemical elevations are necessary in order to explain current symptoms
  - —Mutations/variants identified may be classified as follows (it is important to read the DNA report carefully):
    - Known pathogenic, based on previous clinical reports or in vitro expression studies
    - Known benign variant, also based on previous clinical reports or expression studies
    - Variant of unknown significance, for which adequate information does not exist

AHP: acute hepatic porphyria.

Anderson KE. *Mol Genet Metab*. 2019;128:219-227.

Specialty Referral of Patients With AHP

- Referral is not needed for first- and second-line testing, because these tests are widely available to all primary care, ED, and subspecialty physicians
- Some subspecialty physicians can help with treatments such as intravenous hemin, when necessary
- Patients with an established or strongly suspected diagnosis of AHP should be referred to a porphyria center, such as one of those in the Porphyrias Consortium
  - Confirm the diagnosis and provide genetic counseling
  - Advise on treatment and follow up, eg, hemin, givosiran, GnRH analogs, screening for liver cancer, monitoring of renal function

AHP: acute hepatic porphyria; ED: emergency department; GnRH: gonadotropin-releasing hormone.

Case: 30-Year-Old Woman

- A 30-year-old woman developed abdominal pain, nausea, vomiting, and diarrhea
- She was hospitalized for 2 weeks for a suspected intestinal infection
  - She experienced pain that required intravenous morphine
  - Evaluation, including upper and lower endoscopies, did not establish a definite cause for the symptoms
- Patient gradually improved and was discharged

Case: 30-Year-Old Woman (cont)

- Symptoms recurred ~2 years later
  - Under stress from a divorce
  - Multiple ED visits because of abdominal pain, mental symptoms
  - Admitted to a psychiatric unit with mental status changes, hallucinations
  - Transferred to an ED with abdominal pain
    - Experienced a grand mal seizure
    - Hyponatremic

ED: emergency department.

Question

What testing might have been done at this time?

A. MRI
B. Lumbar puncture
C. Electroencephalography
D. Abdominal ultrasound
E. Urine porphobilinogen and porphyrins

MRI: magnetic resonance imaging.

Question

What testing might have been done at this time?

A. MRI
B. Lumbar puncture
C. Electroencephalography
D. Abdominal ultrasound
E. Urine porphobilinogen and porphyrins

Correct answer = E. Urine porphobilinogen and porphyrins

MRI: magnetic resonance imaging.

Case: 30-Year-Old Woman (cont)

- Admitted to a medical unit
- Evaluation showed:
  - Pulse 120 bpm
  - BP 174/114 mm Hg
  - Disorientation
  - No focal neurological signs

BP: blood pressure.

Case: 30-Year-Old Woman (cont)

- LP normal
- MRI showed multiple areas of subcortical signal abnormalities
- Electroencephalogram abnormal
  - Recurring single and multiple spikes and sharp discharge activity appearing to arise from the left anterior temporal region
- ALT 114 U/L
- AST 94 U/L

ALT: alanine aminotransferase; AST: aspartate aminotransferase; LP: lumbar puncture; MRI: magnetic resonance imaging.

Case: 30-Year-Old Woman (cont)

- Phenytoin started
- Abdominal pain and hyponatremia worsened (sodium 116 mEq/L)
- SIADH attributed to fluoxetine (antidepressant)
- Abnormal HIDA scan
  - Laparoscopic cholecystectomy
  - Gallbladder normal

HIDA: hepatobiliary iminodiacetic acid; SIADH: syndrome of inappropriate antidiuretic hormone secretion.

Case: 30-Year-Old Woman (cont)

- Diagnoses at discharge
  - Alcohol withdrawal
  - Liver disease
- Referred for rehabilitation
- Urine porphyrin measurement ordered by a neurologist before discharge
  - Later reported as “positive”
  - Patient could not be located

Case: 30-Year-Old Woman (cont)

- Symptoms progressed
  - —Stayed with a family member in another state
- Hospitalized with weakness
- Condition progressed
  - —Quadriparesis
  - —Respiratory failure
    - Aspiration pneumonia
- Urinary PBG = 44 mg/24 h (reference range 0-4 mg/24 h)

PBG: porphobilinogen.

Case: 30-Year-Old Woman (cont)

- Harmful drugs (including phenytoin) were stopped
- Treated with intravenous glucose but not hemin
- Improved gradually
- Discharged for physical therapy and rehabilitation

Case: 30-Year-Old Woman (cont)

- Recovered almost completely
  - Residual painful hyperesthesia of LEs
  - Proximal muscle weakness
  - Impaired short-term memory
- Several attacks during the next few years
  - Some during the premenstrual/luteal phase

LE: lower extremity.

Take-home Lessons From This Case

- Classic features of acute porphyria
- Acute porphyria often is not recognized
  - Testing may be done even if the index of suspicion is not high
- Treatment often is not optimal
  - Severe cases should be treated with hemin
- Recovery can be complete or nearly complete

Improving AHP Patient Care: Focusing on Disease-specific Therapy

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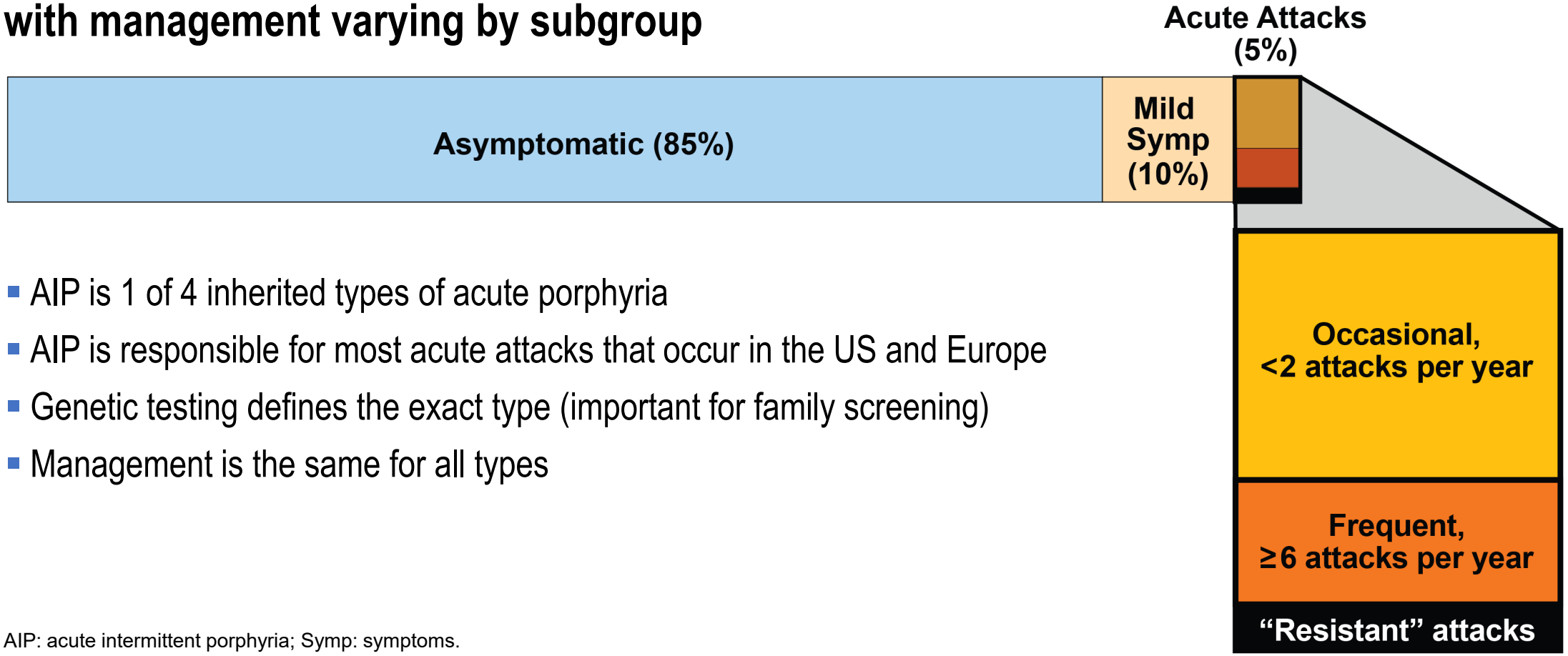
AIP: Clinical Presentation Along a Spectrum

The clinical presentation of AIP covers a spectrum, with management varying by subgroup



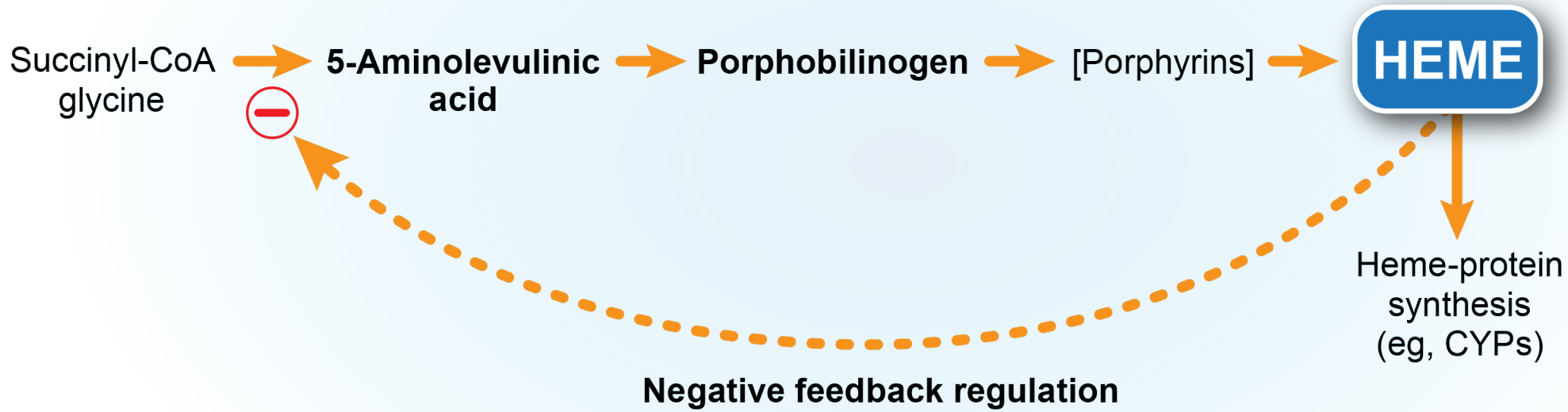
- AIP is 1 of 4 inherited types of acute porphyria
- AIP is responsible for most acute attacks that occur in the US and Europe
- Genetic testing defines the exact type (important for family screening)
- Management is the same for all types

AIP: acute intermittent porphyria; Symp: symptoms.

Bissell DM, et al. *N Engl J Med*. 2017;377:862-872. Bonkovsky HL, et al. *Mol Genet Metab*. 2019;128:213-218.

Management of AIP

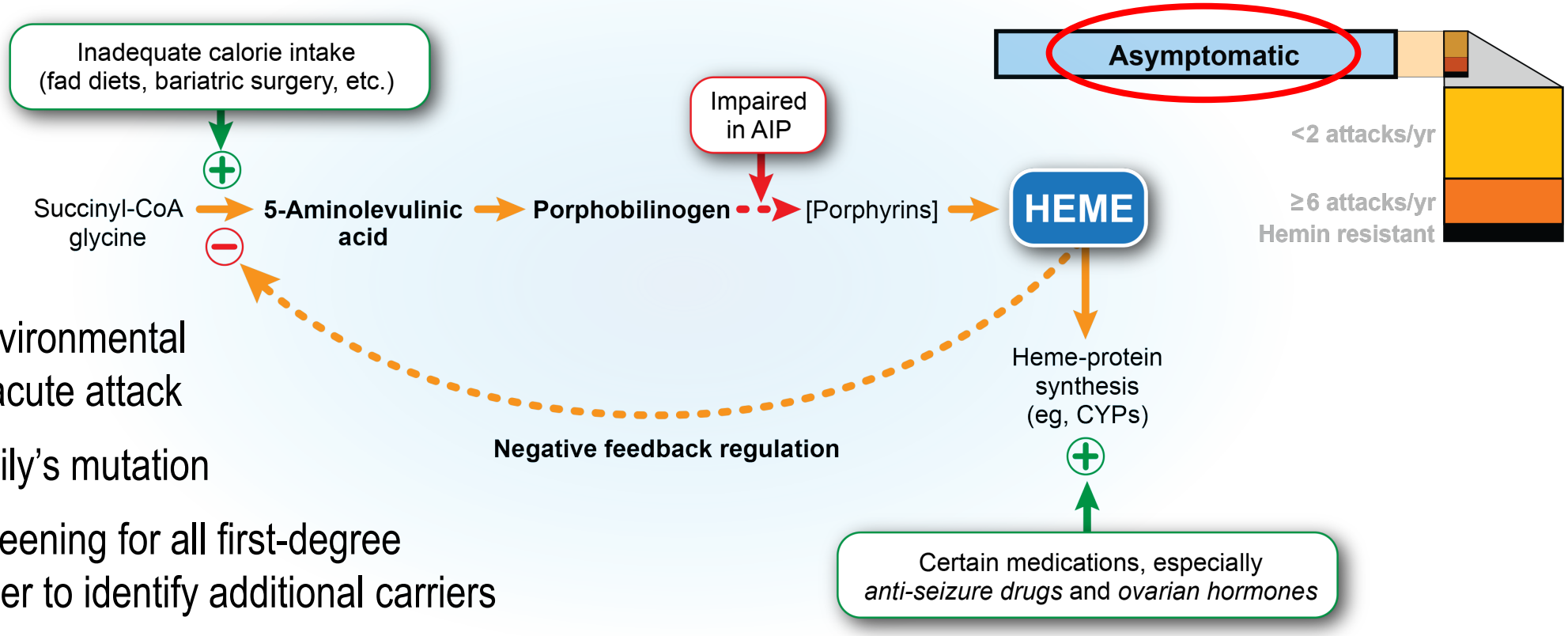
Management of AIP is based on the chemistry and pathobiology of the disease



AIP: acute intermittent porphyria; CoA: coenzyme A; CYP: cytochrome P.
Bissell DM, et al. *N Engl J Med*. 2017;377:862-872.

Health Maintenance for Asymptomatic Patients

Health maintenance for the carrier population ***without symptoms***



- Educate on environmental triggers of an acute attack
- Define the family's mutation
- Encourage screening for all first-degree relatives in order to identify additional carriers

AIP: acute intermittent porphyria; CoA: coenzyme A; CYP: cytochrome P.

Bissell DM, et al. *N Engl J Med*. 2017;377:862-872. American Porphyria Foundation. https://porphyriafoundation.org/

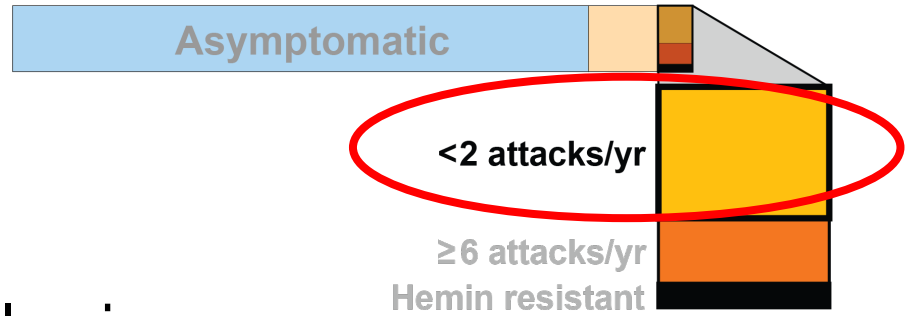
Medications and Porphyria

	Anticonvulsants and Hypnotics	Other Drugs	
Safe	Gabapentin Propofol Magnesium sulfate Diazepam Chloral hydrate Bromides	Acetaminophen Aminoglycosides Aspirin Codeine Colchicine Dexamethasone	Furosemide Ibuprofen Insulin Meperidine Morphine Penicillins
Unsafe	Barbiturates Carbamazepine Glutethimide Ethosuximide Phenytoin Valproic acid	α-Methyldopa Diclofenac Ergot preparations Sulfonamides Griseofulvin Pentazocine Pyrazinamide Estrogen/progesterone	

Comprehensive lists are found in the Porphyria Drug Safety database (http://porphyriadrugs.com) and the Drug Database for Acute Porphyria (http://www.drugs-porphyria.org/index.php).
Anderson KE, et al. *Ann Intern Med*. 2005;142(6):439-450.

Treatment for Acute Attacks

- Remove environmental triggers
- Provide fluid resuscitation (dextrose in saline) while watching for hyponatremia
- Relieve pain (with, eg, IV hydromorphone)
- Evaluate for other causes of nausea and abdominal pain
- Collect a urine sample to measure PBG and creatinine
- If the evaluation points to AIP, infuse IV heme (hemin)



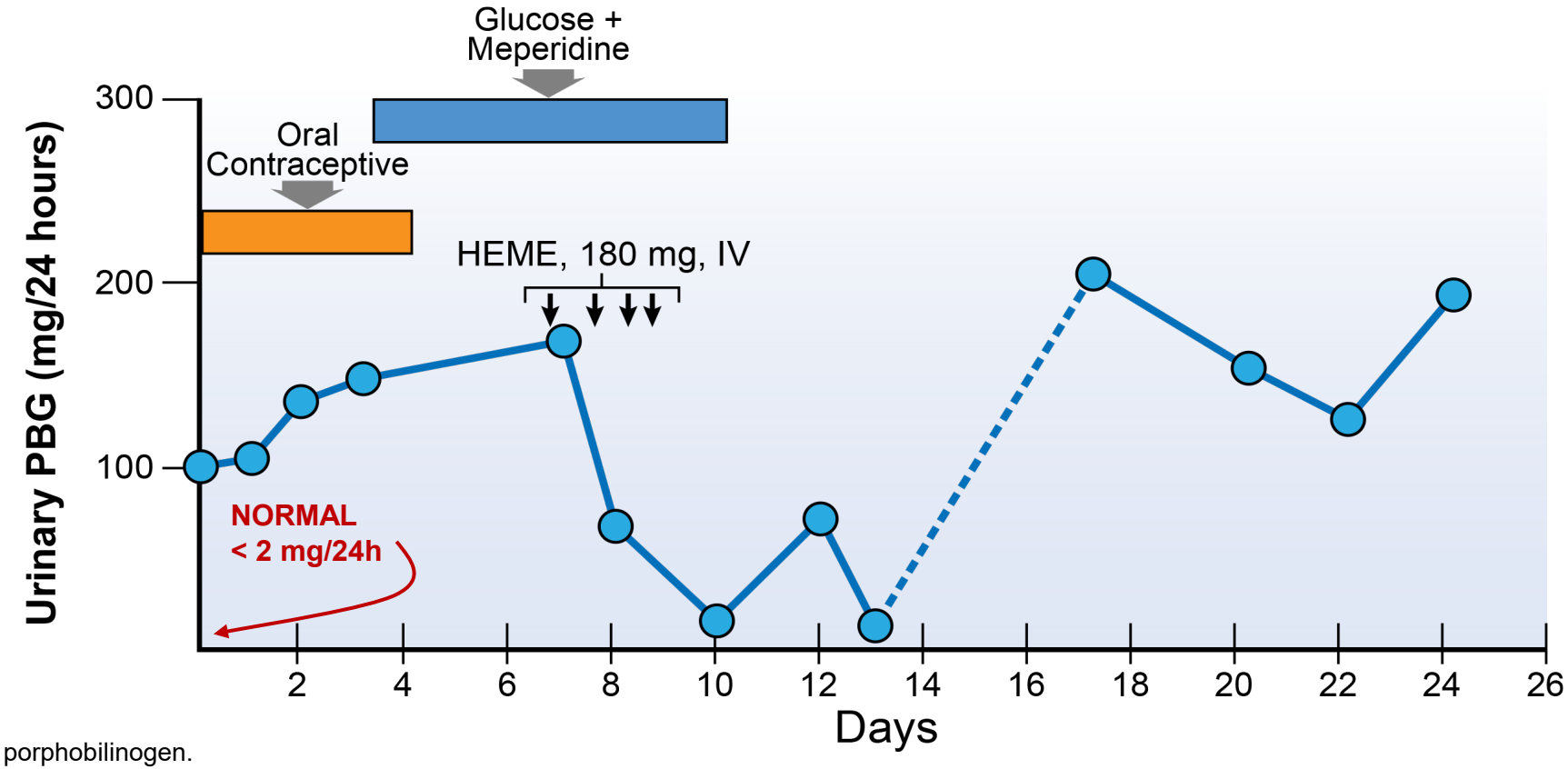
AIP: acute intermittent porphyria; IV: intravenous; PGB: porphobilinogen.

Anderson KE, et al. *Ann Intern Med*. 2005;142(6):439-450. Bissell DM, et al. *N Engl J Med*. 2017;377:862-872.

IV Hemin

Biochemical Response to IV Hemin

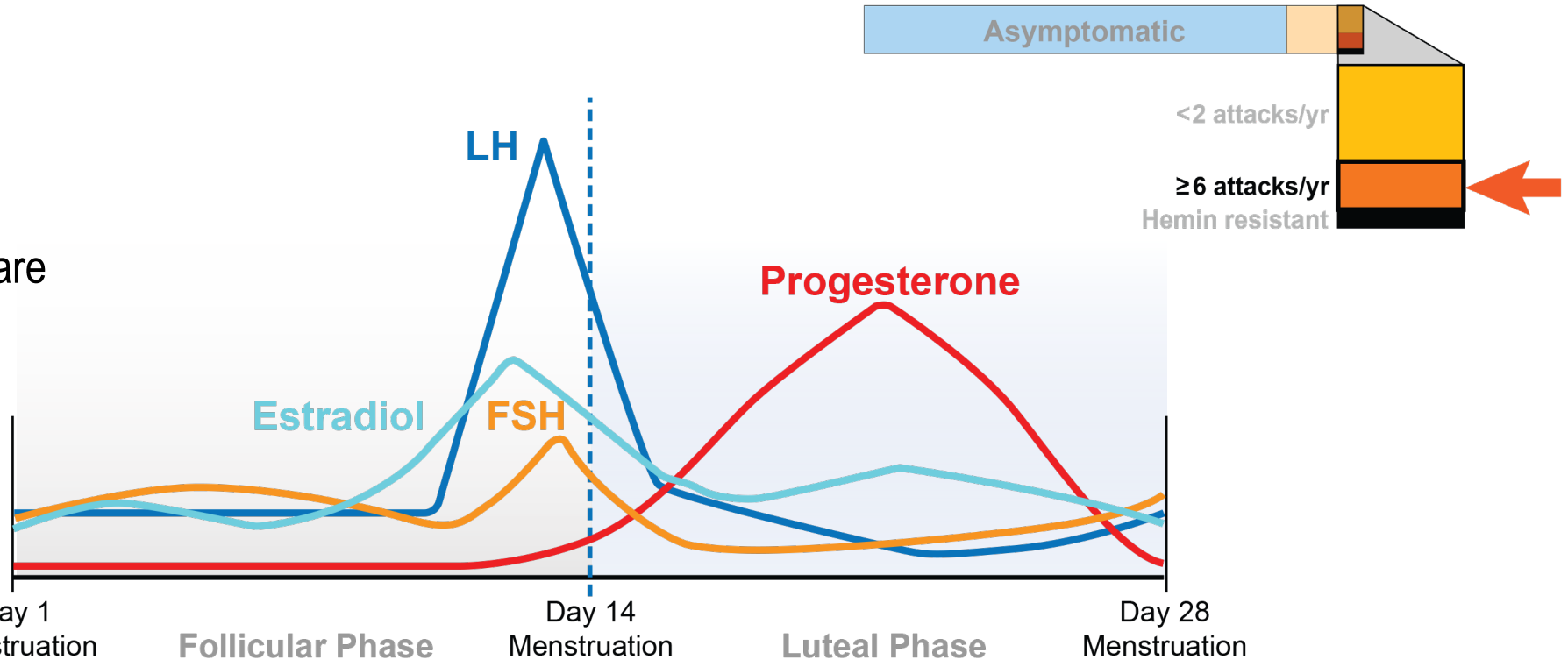
*Note that PBG begins to decrease **48 hours** after the initial dose of hemin*



IV: intravenous; PBG, porphobilinogen.
Image courtesy of D. Montgomery Bissell, MD.

Prophylaxis for Patients Who Experience Multiple Attacks per Year

- The main subpopulation with frequent attacks is primarily younger women (90%)
- Two types of attacks
  - Attacks related to the ovulatory cycle
  - Frequent attacks that are unrelated to the cycle



Reed BG, Carr BR. The normal menstrual cycle and the control of ovulation. Updated August 5, 2018. In: Feingold KR, et al., eds. Endotext [Internet]. MDText.com; 2000-. https://www.ncbi.nlm.nih.gov/books/NBK279054/. Reproduced for educational purposes only.

Prophylaxis for Patients Who Experience Multiple Attacks per Year (cont)

- **Treatment option for cycle-related attacks**
  - **GnRH agonist**
    - Leuprolide, goserelin, etc., to suppress ovulation
    - Side effects: symptoms of menopause
    - *Hormone contraceptives can provoke acute attacks and are avoided*

- **General treatment**
  - **Givosiran**
    - ALA synthase blocker, given SQ monthly
    - Side effects: increased ALT, injection site reactions
  - **Hemin**
    - IV, administered 7-10 days before the expected onset of menstruation
    - Side effects: phlebitis, central catheter issues, iron loading

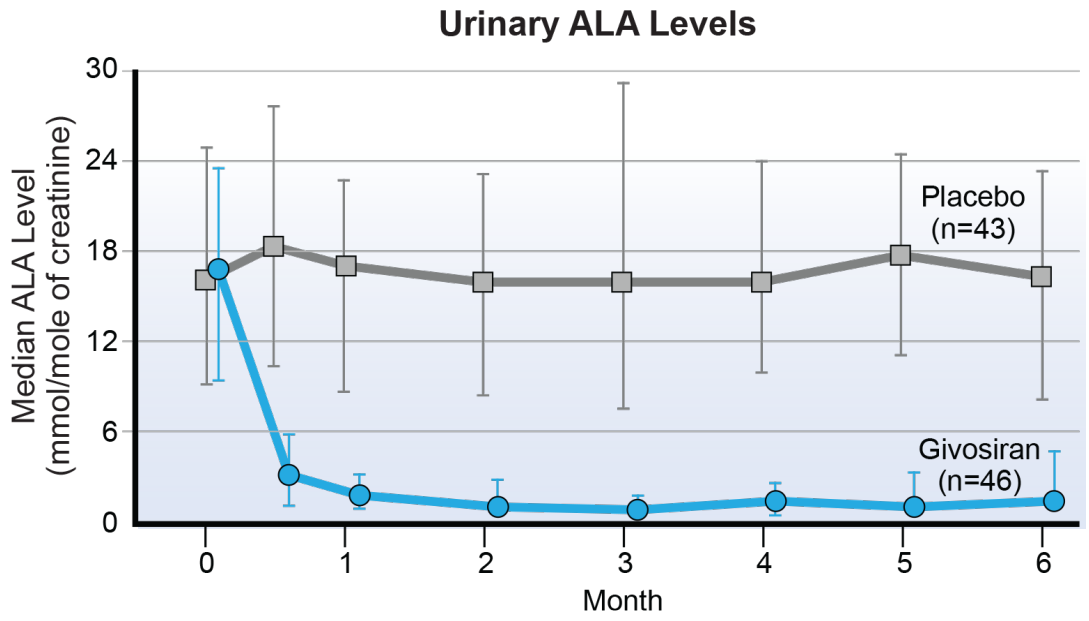
ALA: 5-aminolevulinic acid; ALT: alanine aminotransferase; GnRH: gonadotropin-releasing hormone; IV: intravenous: SQ: subcutaneously.

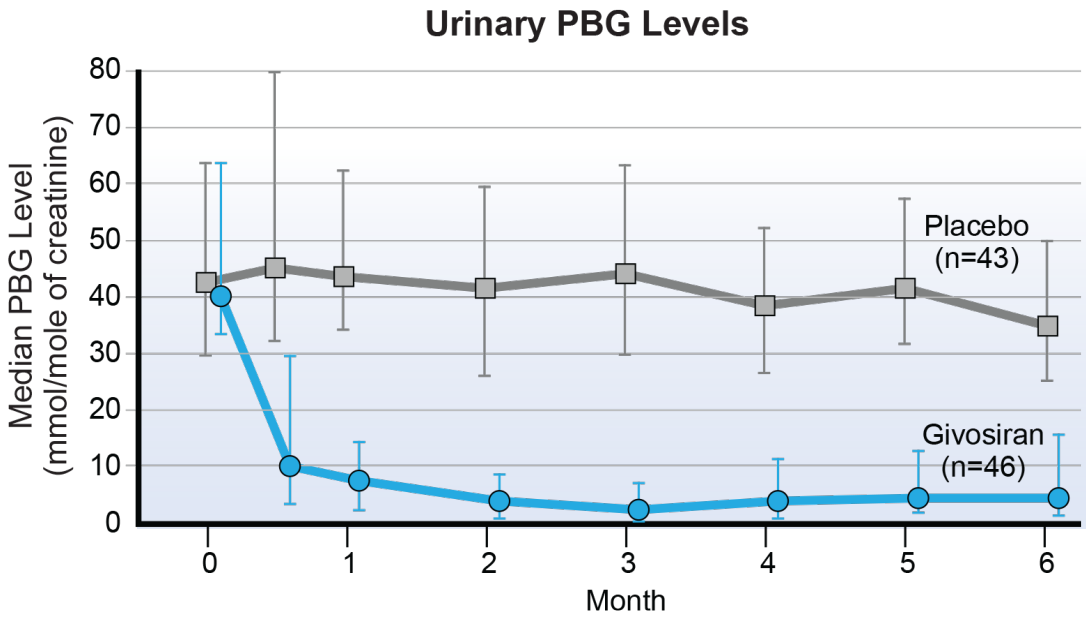
Stein P, et al. *Ann Clin Biochem.* 2013;50(pt 3):217-223. Balwani M, et al. *N Engl J Med*. 2020;382:2289-2301.

Givosiran

A new RNA-based drug that targets hepatocytes

- Causes ALA synthase mRNA to degrade and reduces ALA production

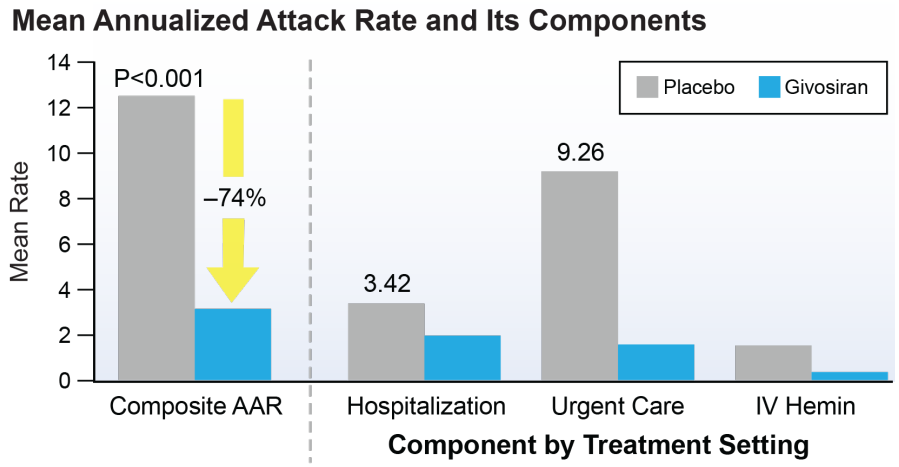


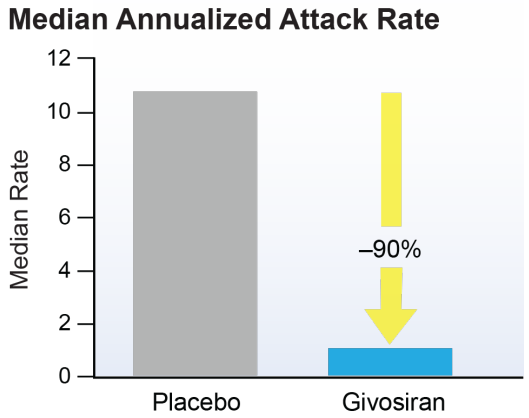


ALA: 5-aminolevulinic acid; mRNA, messenger RNA; PBG: porphobilinogen.

Givosiran (cont)

- Positives
  - Very effective at preventing acute flares of AIP
  - SQ administration; no need for a visit to an infusion center
  - A single injection has a prolonged effect (at least 1 month)
  - Side effects have been minor except for one reported case of anaphylaxis
- Negatives
  - Not approved for use during pregnancy (data are lacking)
  - Expensive ($40,000 per injection)

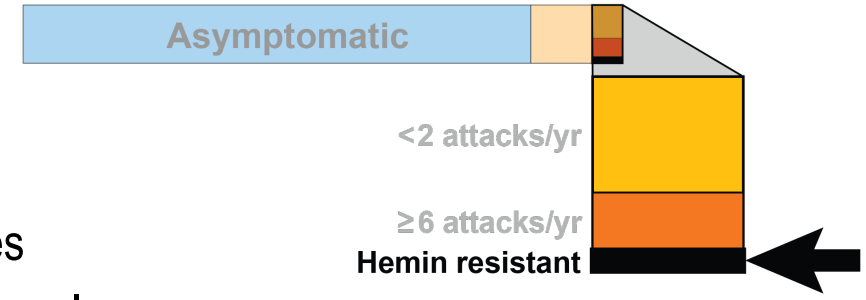




AAR: annualized attack rate; AIP: acute intermittent porphyria; IV: intravenous; SQ: subcutaneous.

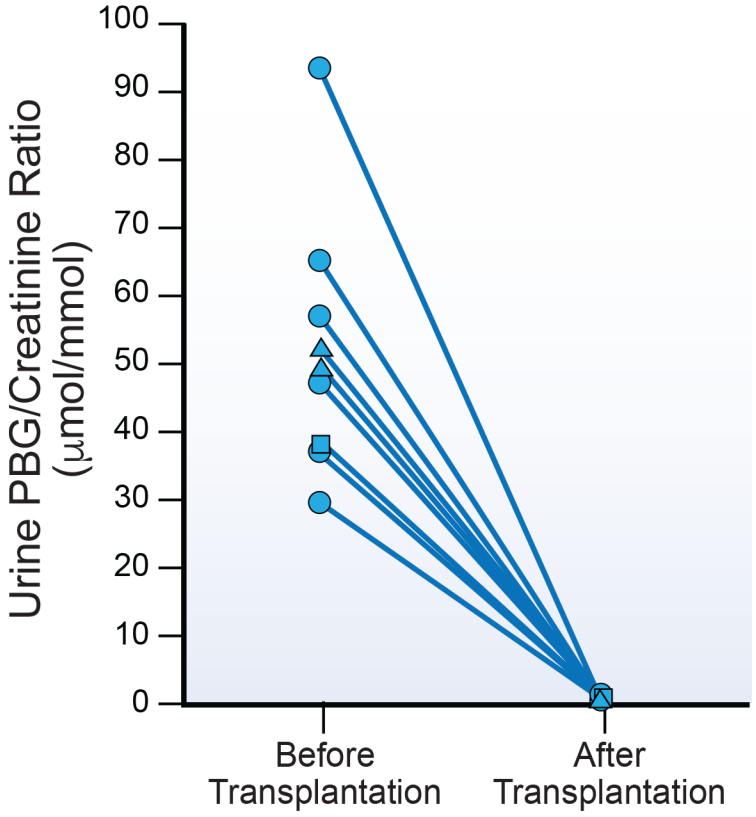
Hemin "Resistance"

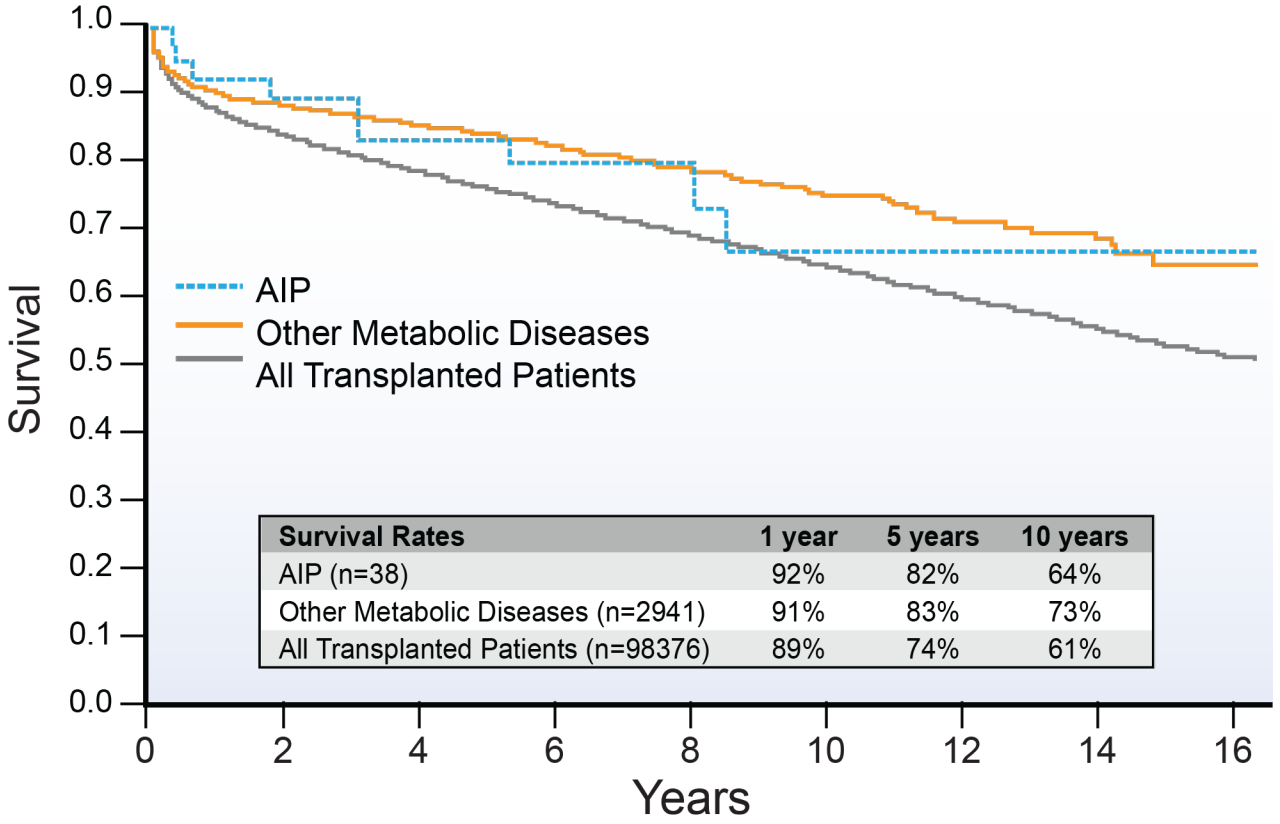
- Minimal clinical or biochemical response to hemin infusion
- Possible causes
  - —Use of decayed hemin
    - The product comes as a stable powder. Once in a solution, however, it becomes **unstable** and must be infused within 30 minutes
  - —The patient is a porphyria carrier whose pain is due to something else (eg, narcotic withdrawal)
  - —Misdiagnosis based on misunderstood urine tests (a fairly frequent occurrence)
- Treatment of *true* hemin resistance in a patient with frequent acute flares of porphyria
  - —Givosiran, an RNA-based inhibitor of ALA synthase
  - —Liver transplantation



ALA: 5-aminolevulinic acid.

Liver Transplantation for Acute Porphyria





Survival Rates	1 year	5 years	10 years
AIP (n=38)	92%	82%	64%
Other Metabolic Diseases (n=2941)	91%	83%	73%
All Transplanted Patients (n=98376)	89%	74%	61%

AIP: acute intermittent porphyria; PBG: porphobilinogen.

Dowman JK, et al. *Liver Transpl*. 2012;18:195-200. Lissing M et al. *Liver Transpl*. 2021;27:491-501.

Challenges With Liver Transplant for AIP

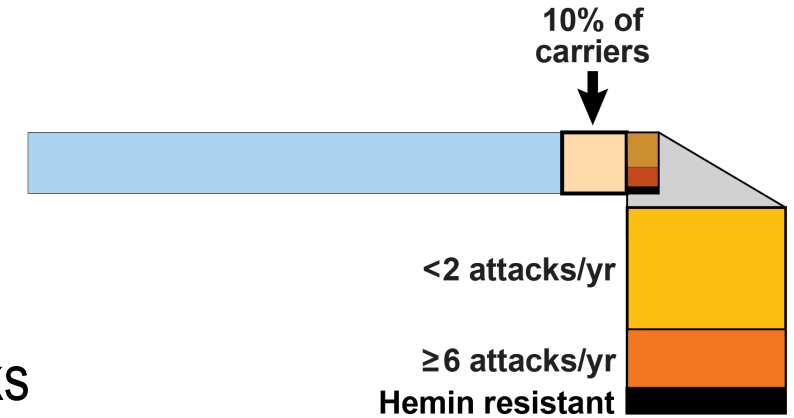
- To date, approximately 40 patients have received a liver transplant for AIP
- Candidates for transplant are patients who have not responded to prolonged medical treatment and who have poorly controlled pain and progressive neuropathy
- The challenge is timing:
  - *Too early*: Spontaneous remission of AIP is possible and, for most patients, is the preferred outcome
  - *Too late*: Patients who are, for any reason, debilitated and immobile (bedridden or on a respirator) will be deemed "too sick" for transplant
- Firm guidelines do not exist
  - AIP is not a recognized indication for liver transplant because liver function typically is good to excellent
  - Transplant may be possible only if a live donor is available
  - The timing of transplant is critical, but at present it represents the best judgment of the individual physician

AIP: acute intermittent porphyria.

Lissing M, et al. *Liver Transpl*. 2021;27:491-501.

AIP Carriers Who Experience Chronic Symptoms Without an Acute Attack

- What about treatment of AIP carriers who have chronic symptoms that never reach the level of an acute attack?
  - Some carriers report chronic or recurring periods of fatigue requiring bed rest, along with brain fog, loss of appetite, insomnia, and stress
  - Urine ALA and PBG are elevated in most cases



- The givosiran registration study focused on overt acute attacks but also found evidence for relief of subacute symptoms
  - Although these results are promising, a double-blind randomized trial is necessary before givosiran can be recommended for treating chronic subacute symptoms
  - Given the nonspecific nature of the concerns, a large placebo response is likely

AIP: acute intermittent porphyria; ALA: 5-aminolevulinic acid; PBG: porphobilinogen.

Balwani M, et al. *N Engl J Med*. 2020;382:2289-2301.

Givosiran: Attractive for Preventing Chronic Organ Injury

- Patients are at risk of chronic injury to the nervous system, kidneys, or liver and of developing primary liver cancer
- However:
  - —A prospective study is necessary
  - —The cost-to-benefit ratio of givosiran is unknown in this context
    - What is the optimal time to start prophylactic givosiran with respect to the stage of tissue injury?
    - What is the natural history of chronic organ damage due to AIP?
      - Current data suggest that organ injury remains subclinical and that a few patients progress to neural disability, kidney transplant, or liver cancer
    - How do we select the patients at highest risk?
  - —Safety of continuous givosiran treatment beyond 2 years is unknown; data collection is ongoing

AIP: acute intermittent porphyria.

Balwani M, et al. *N Engl J Med*. 2020;382:2289-2301.

Case: 24-Year-Old Woman With Genetically Confirmed AIP

- Initial presentation
  - —Onset occurred several months after starting a keto diet for weight control
  - —Felt anxious and depressed for a week
  - —Developed nausea and vomiting with abdominal pain that progressed over 2 weeks to deep, gnawing pain (intensity, 10 of 10)
- A positive family history suggested a diagnosis of AIP
  - —Paternal grandmother was believed to have porphyria
- Urine PBG was elevated at 80 mg/g creatinine (normal value, <2 mg/g creatinine)
- Patient was hospitalized and rehydrated with glucose and saline

AIP: acute intermittent porphyria; PBG: porphobilinogen.

Question

Which agent would you use to treat this patient?

A. GnRH
B. Givosiran
C. IV hemin
D. β-Blocker

GnRH: gonadotropin-releasing hormone; IV: intravenous.

Question

The patient read that a high-carbohydrate diet is helpful for porphyria but is worried about gaining weight. What would you recommend?

A. A high-carbohydrate diet and regular exercise

B. A balanced diet with total calories calculated in order to maintain current weight or slowly reduce weight

C. 300 g of 10% IV glucose in addition to IV hemin

IV: intravenous.

Question

The patient read that a high-carbohydrate diet is helpful for porphyria but is worried about gaining weight. What would you recommend?

A. A high-carbohydrate diet and regular exercise

B. A balanced diet with total calories calculated in order to maintain current weight or slowly reduce weight

C. 300 g of 10% IV glucose in addition to IV hemin

Correct answer = B. A balanced diet with total calories calculated in order to maintain current weight or slowly reduce weight

IV: intravenous.

Interdisciplinary Care of Patients With AHP

- Acute porphyria is a multisystem disease requiring an interdisciplinary approach
- Specialists who work with a porphyria specialist and their roles:
  - ED staff: improve the early diagnosis and treatment of AIP
  - GI providers: raise awareness of possible AIP in patients labeled as having IBS
  - GYN providers: encourage screening of young women with PMS
  - Geneticists: advise patients on the risks and benefits of genetic screening and pregnancy
  - Neurologists: help to better understand the basis for symptoms in AIP

AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ED: emergency department; GI: gastroenterology; GYN: gynecology; IBS: irritable bowel syndrome; PMS: premenstrual syndrome.

Summary

Management of acute porphyria involves **education**, **prevention**, and **acute treatment**

- **Education** for all patients about environmental triggers for acute attacks
  - Especially important for asymptomatic carriers who are identified by genetic screening of families with a member who has acute porphyria
- **Prevention** among patients with frequent acute attacks by using givosiran, hemin (off-label), or a GnRH agonist
- **Acute treatment** for patients during an attack by using hemin or givosiran (off-label)

GnRH: gonadotropin-releasing hormone.