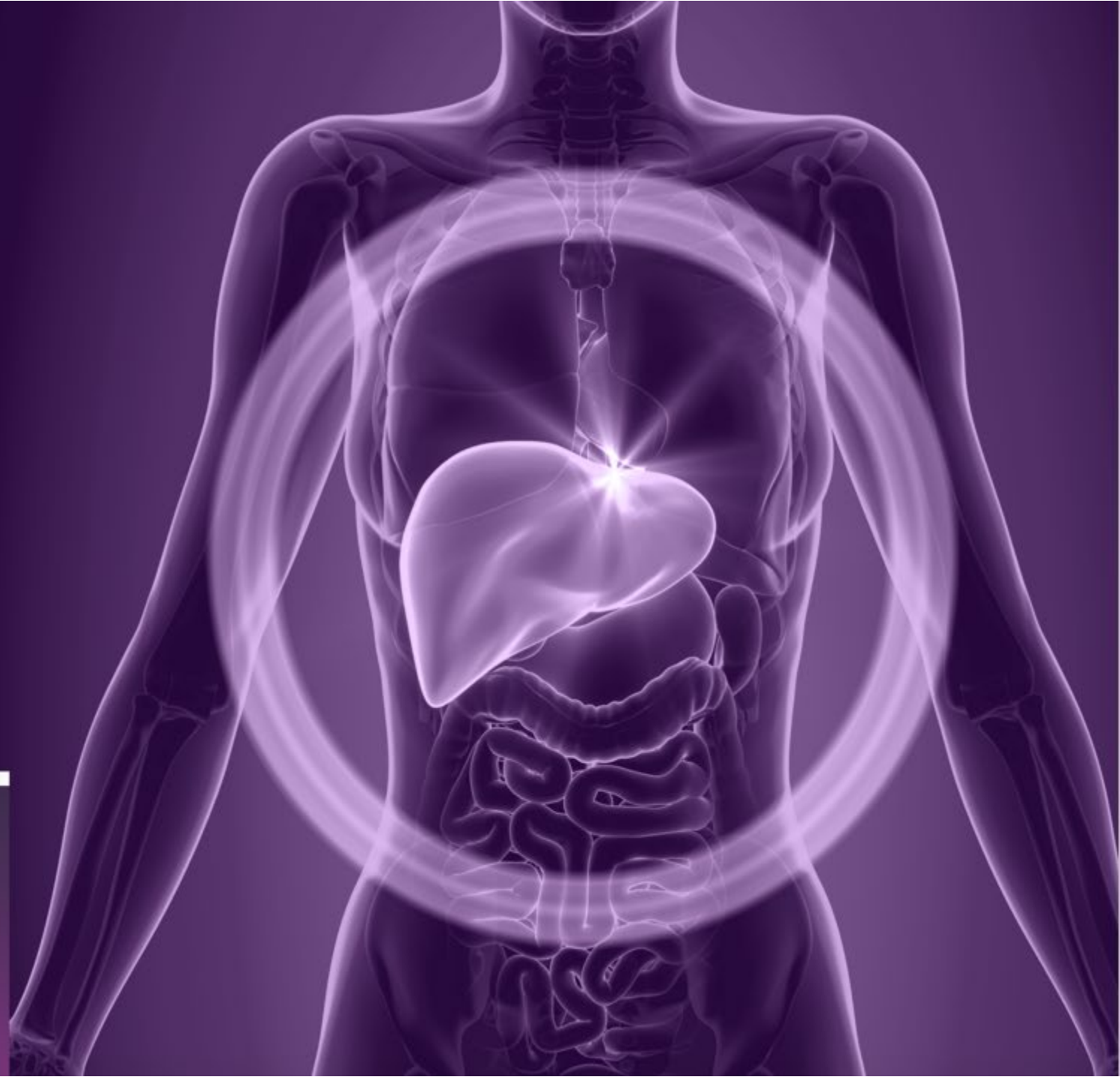


UNMASKING THE 'LITTLE IMITATOR':

IDENTIFYING AND MANAGING
ACUTE HEPATIC PORPHYRIA
IN THE OB/GYN SETTING



Faculty

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Winston Salem, NC



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

PROGRAM OVERVIEW

Many women experience abdominal and pelvic pain related to their menstrual cycle or endometriosis. Yet for some women, these symptoms are due to a group of inherited diseases known as acute hepatic porphyria (AHP). On average, patients spend 15 years misdiagnosed and undergoing numerous medical tests and visits with specialists. This activity will explore how to differentially diagnose patients with unexplained pelvic pain, strategies for confirming a suspected diagnosis of AHP, and available treatments options to ensure early diagnosis and optimal outcomes.

TARGET AUDIENCE

This initiative is intended for obstetrics/gynecologic (OB/GYN) physicians, nurses, physician assistants and other healthcare professionals assessing patients in the OB/GYN 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 AHP as a cause of severe abdominal/pelvic pain among women
- **IDENTIFY** signs and symptoms suggestive of AHP that may present in women seeking OB/GYN care
- **DEFINE** appropriate strategies to screen and diagnose AHP among OB/GYN patients
- **RECOGNIZE** the impact that the menstrual cycle- and medication-induced hormonal changes have on AHP attacks
- **ASSESS** the clinical utility of disease-specific therapies for preventing AHP attacks in women
- **PROPOSE** interdisciplinary strategies to individualize clinical management of AHP in the OB/GYN setting




Agenda

- Introduction
- **Recognizing Potential AHP in the OB/GYN Setting: Clinical Assessment**
- **Strategies for Screening AHP and Reaching a Differential Diagnosis**
- **Improving AHP Management in Women: Identifying and Mitigating Triggers and Implementing Disease-Specific Therapy**
- Question and Answer



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1.5 ANCC contact hours



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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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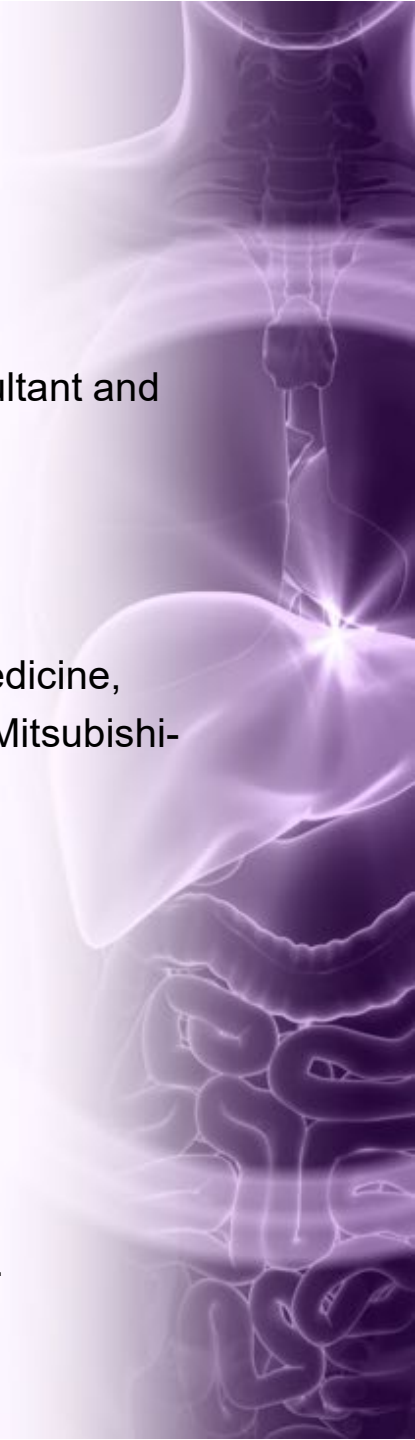
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Recognizing Potential AHP in the OB/GYN Setting

Herbert L. Bonkovsky, MD

Director, Liver and Metabolic Disorders Laboratory
Professor of Medicine and Molecular Medicine &
Translational Research
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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 Porphyrrias According to Main Site of Overproduction

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



Classification of Porphyrrias

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



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



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**



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



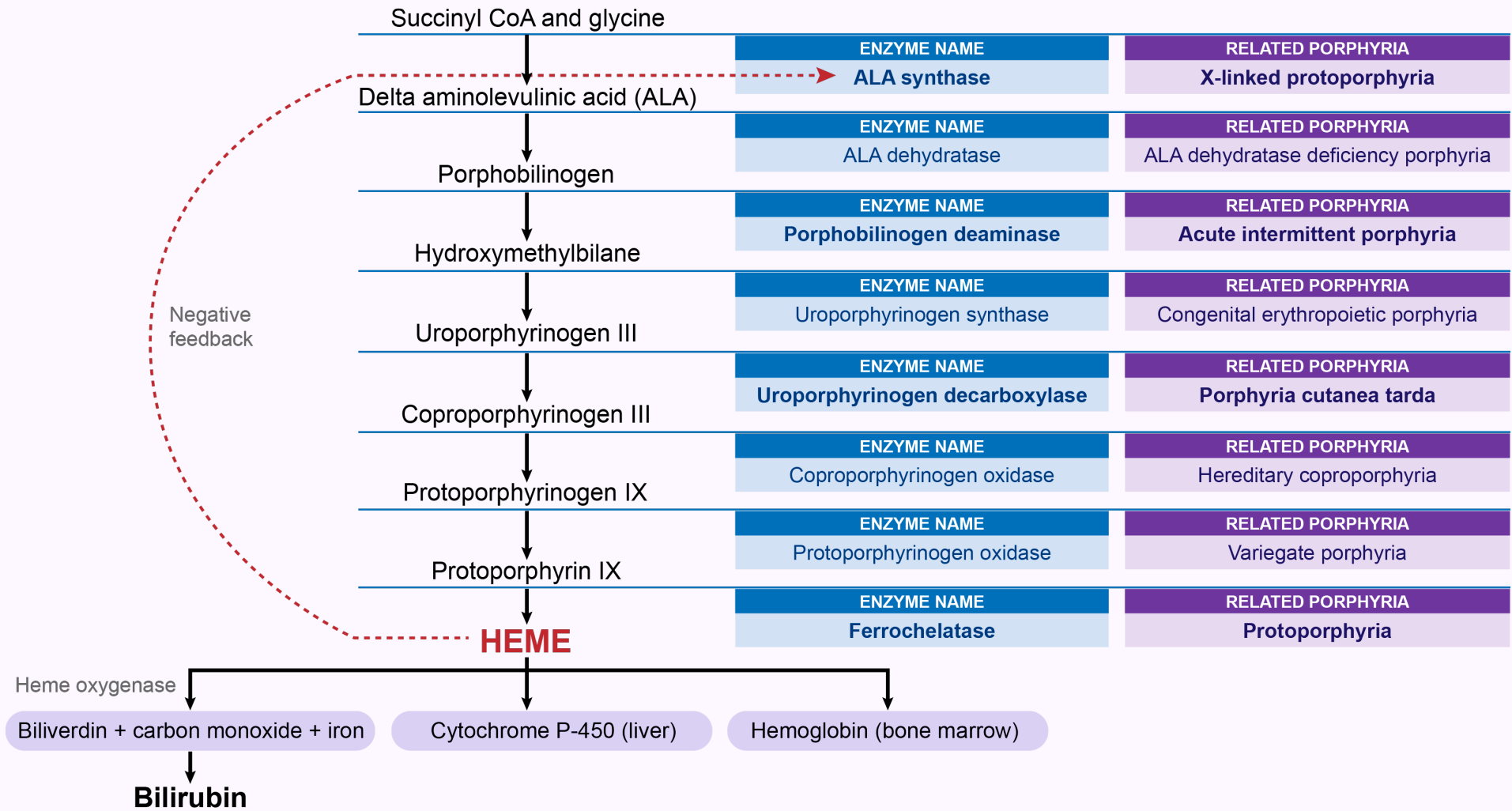
Overview of Mammalian Heme Synthesis

- 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**

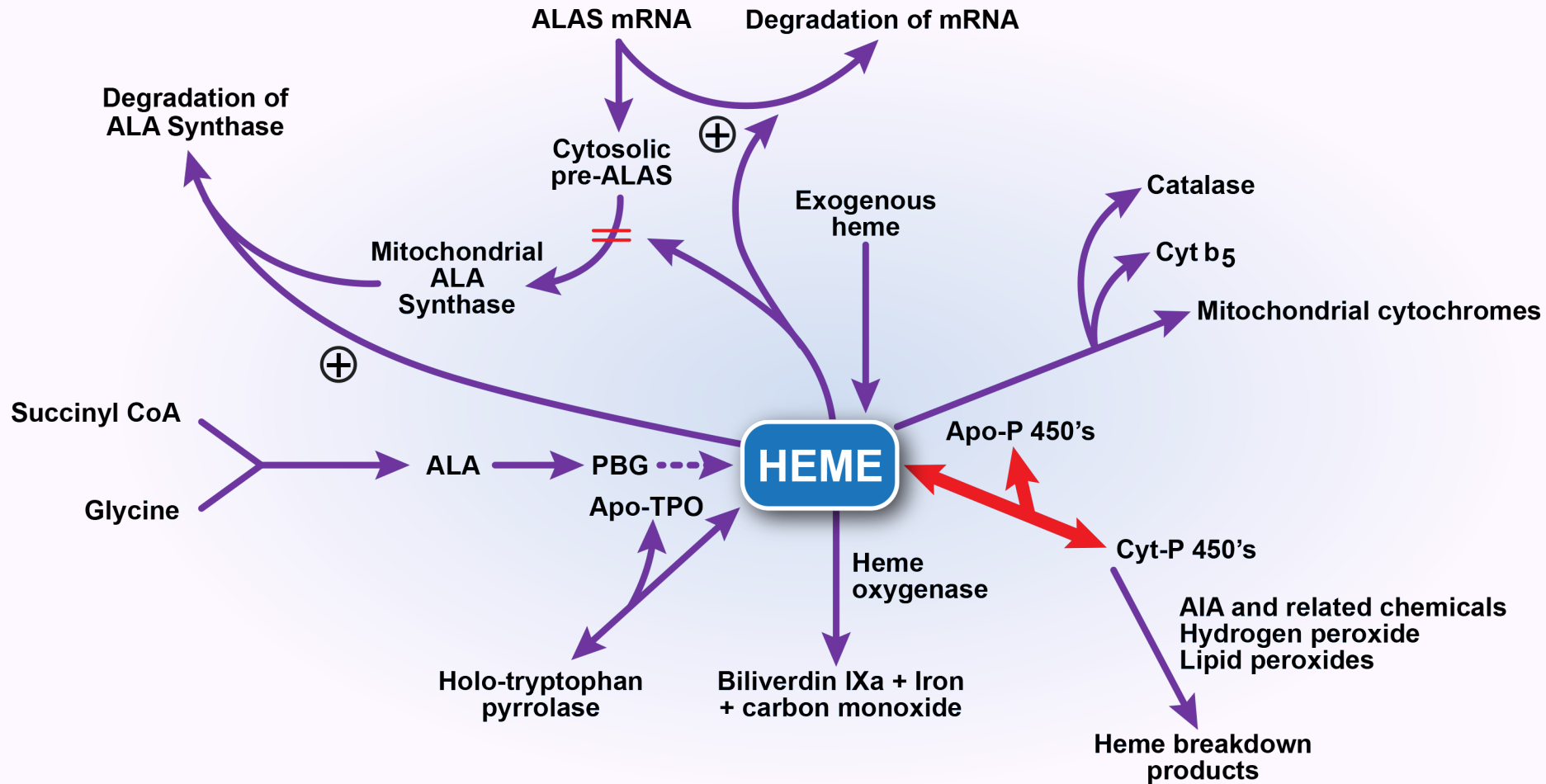
ALA: 5-aminolevulinic acid; CYP: cytochrome P.

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



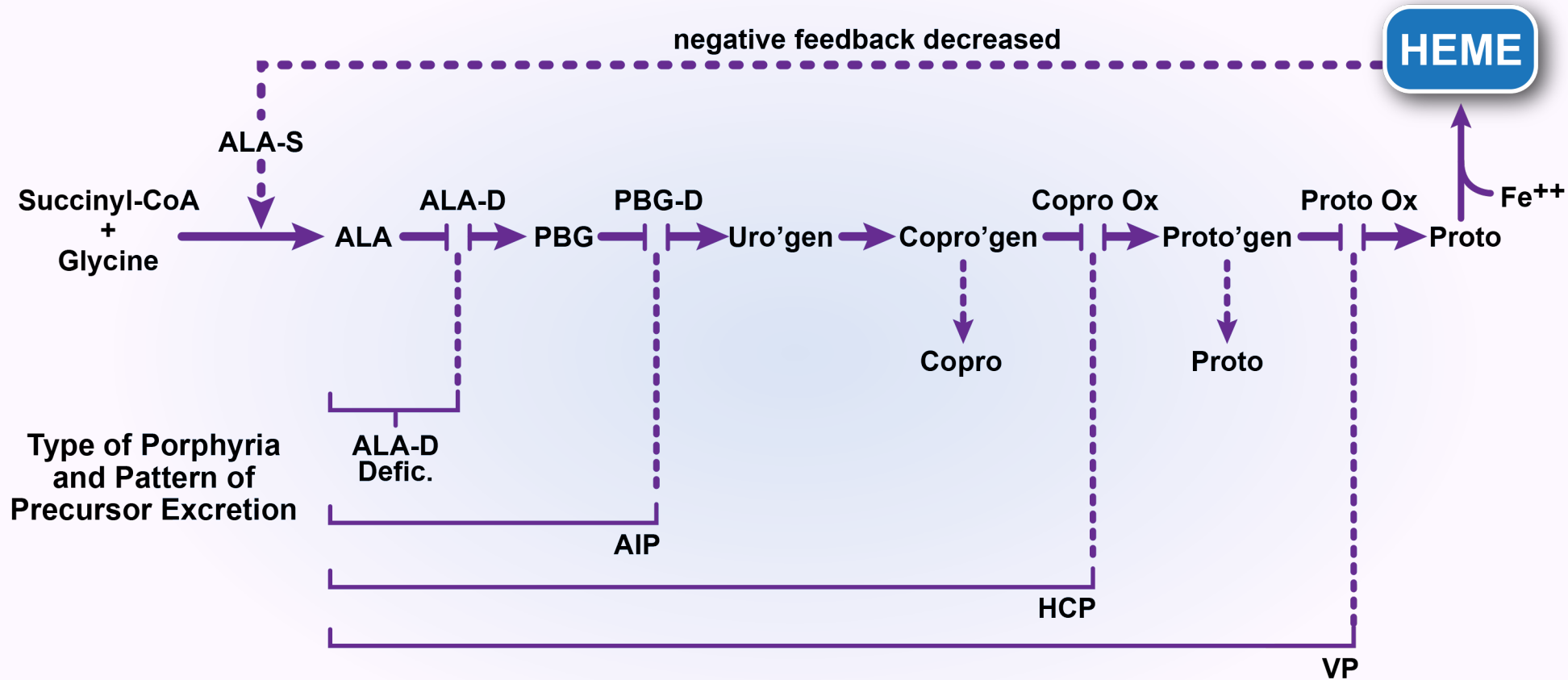
Regulation of Hepatic Heme Metabolism



ALA: 5-aminolevulinic acid; ALAS: 5-aminolevulinic acid synthase-1; Apo-P: apolipoprotein P; APO-TPO: apolipoprotein tryptophan; Cyt b₅: cytochrome b₅; Cyt P450: cytochrome P450; PBG: porphobilinogen.
 Courtesy of H.L. Bonkovsky, MD.



Metabolic Defects and Patterns of Precursor Excretion in Acute Porphyrrias



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 coproporphyrria; Ox: oxidase; PBG: porphobilinogen; PBG-D: porphobilinogen deaminase; VP: variegate porphyria. Courtesy of H.L. Bonkovsky, MD.

Selected Features of the 4 Acute Porphyrrias, 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**



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)

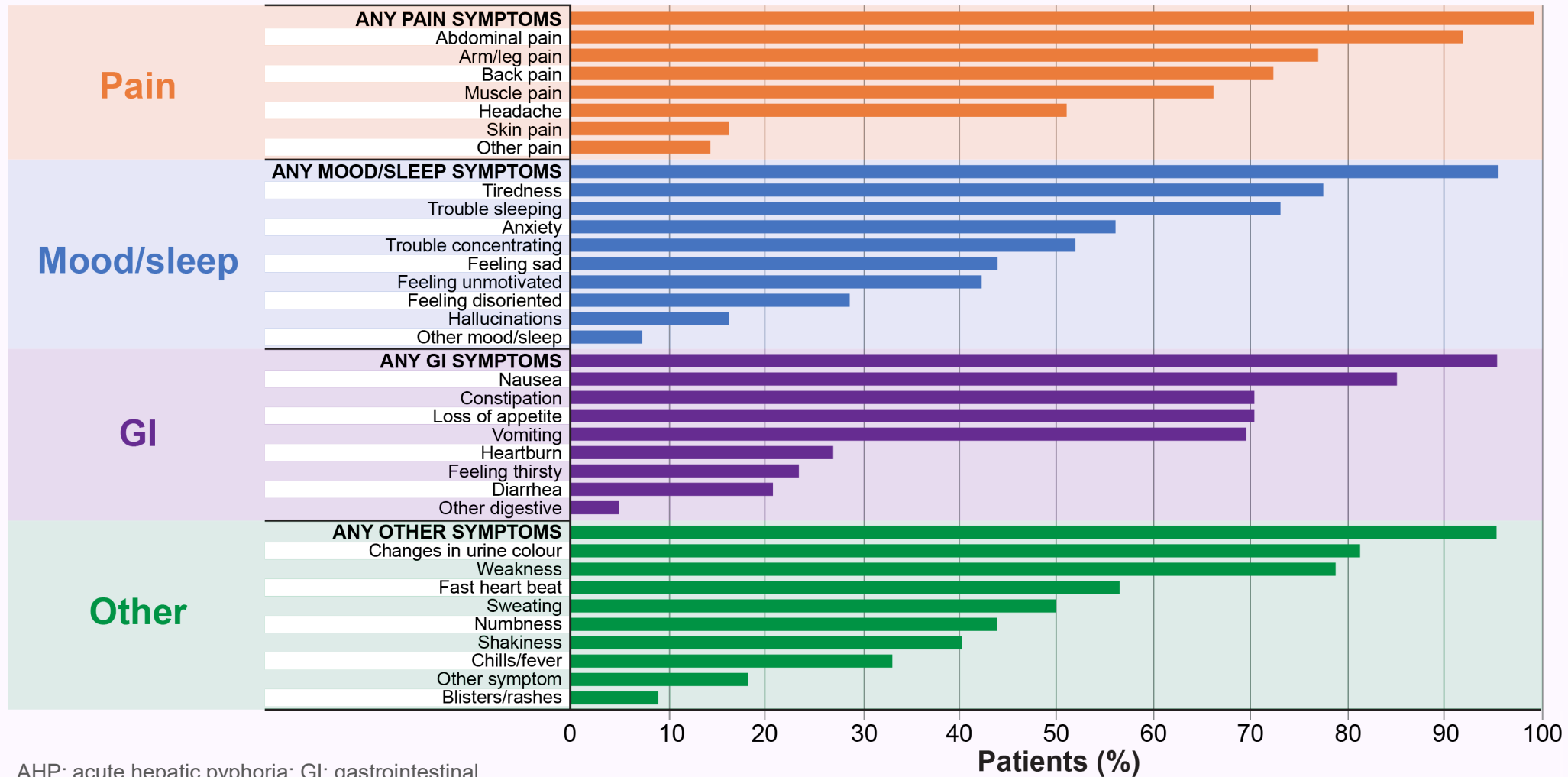
CN: cranial nerve; CNS: central nervous system.

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



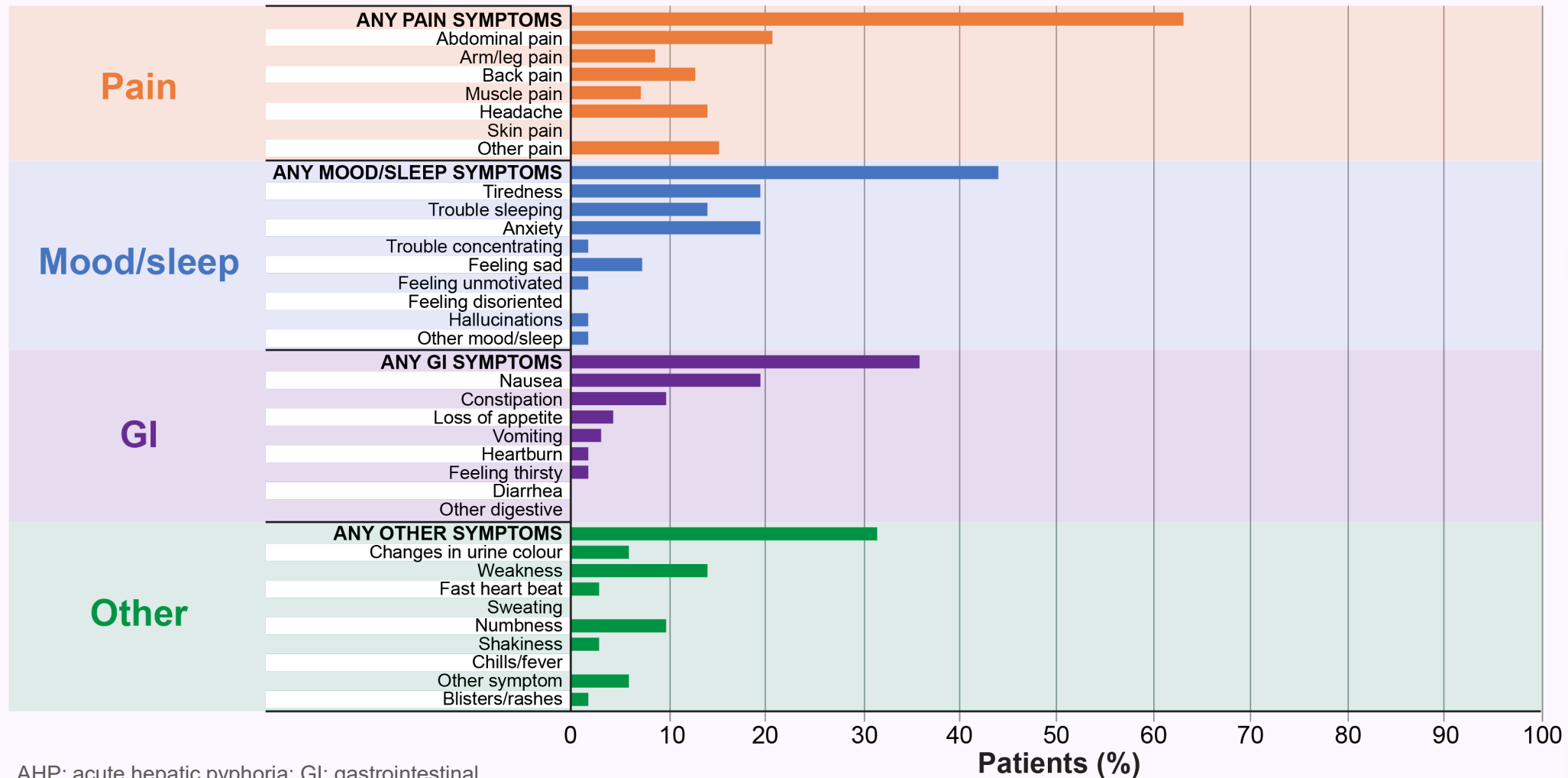
Clinical Features of Acute AHP

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



Clinical Features of Chronic AHP

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



Conclusions

- Porphyrrias are caused by defects in the heme biosynthetic pathway
- Acute hepatic porphyrias are primarily autosomal dominant
 - Attacks occur more frequently in women
 - Men and women of any ethnicity can be affected
- 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



Screening for AHP as Part of a Differential Diagnosis

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Galveston, TX



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

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 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

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.

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



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

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

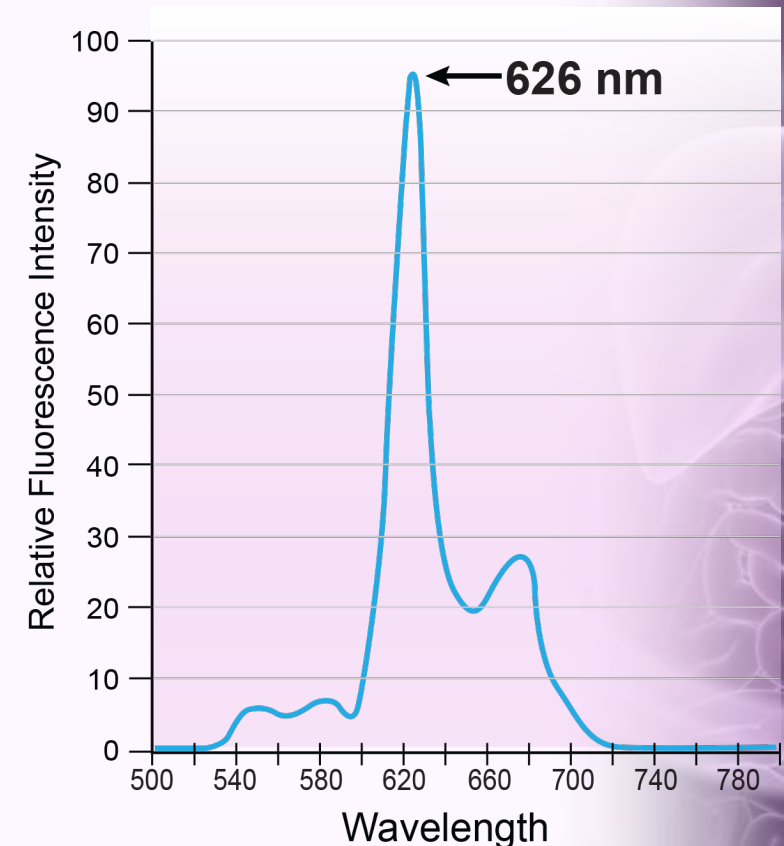
AIP: acute intermittent porphyria; HCP: hereditary coproporphyria; VP: variegate porphyria.
Pischik E, et al. *Appl Clin Genet*. 2015;8:201-214.

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.

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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

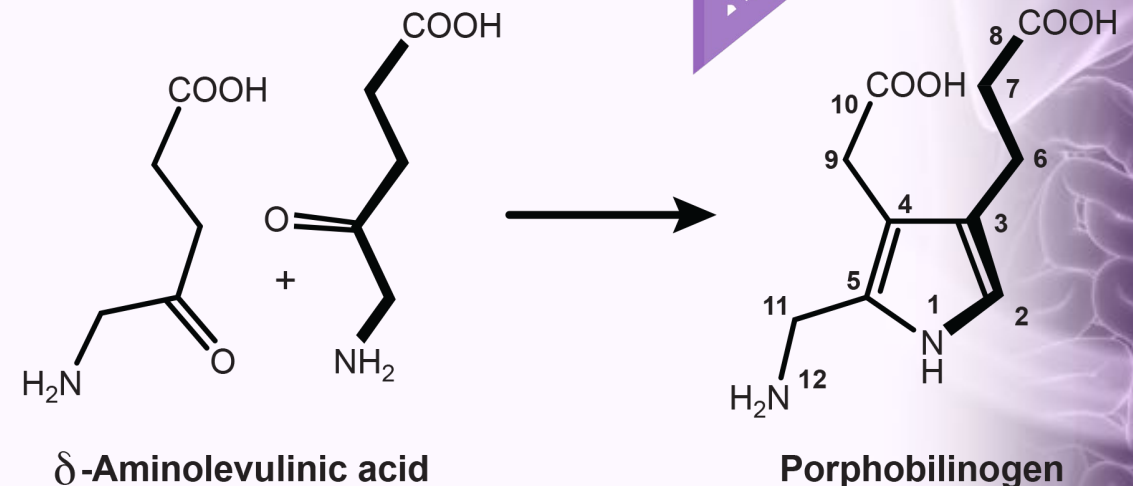


Porphyrin Precursors and Porphyrins

- 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**



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

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



Case: 30-Year-Old Woman

- A 30-year-old woman developed abdominal pain, nausea, vomiting, and diarrhea
- Pregnancy test was negative
- 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



Question

What testing might have been done at this time?

- A. MRI
- B. Lumbar puncture
- C. Electroencephalogram
- D. Pelvic exam and ultrasound
- E. Urine porphobilinogen and porphyrins



Question

What testing might have been done at this time?

- A. MRI
- B. Lumbar puncture
- C. Electroencephalogram
- D. Pelvic exam and ultrasound
- E. Urine porphobilinogen and porphyrins

Correct answer: E. Urine porphobilinogen and porphyrins



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



Case: 30-Year-Old Woman (cont)

- LP normal
- Pelvic exam normal; ultrasound showed small cyst on the right ovary
- 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



Case: 30-Year-Old Woman (cont)

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



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)



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 the LEs
 - Proximal muscle weakness
 - Impaired short-term memory
- Several attacks during the next few years
 - Some during the premenstrual/luteal phase



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 Management in Women: Identifying and Mitigating Triggers and Implementing Disease-Specific Therapy

D. Montgomery Bissell, MD

Professor Emeritus, Medicine

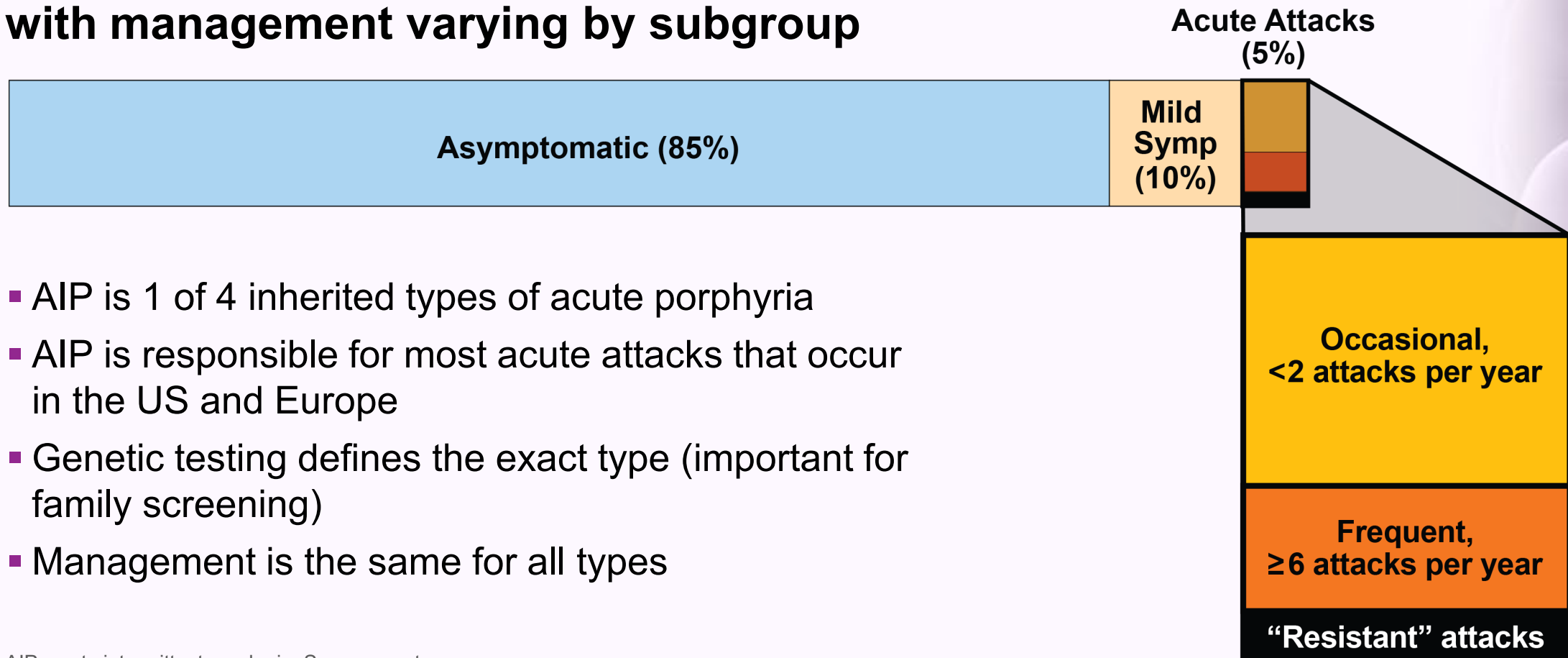
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University of California, San Francisco



AIP: Clinical Presentation Along a Spectrum

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



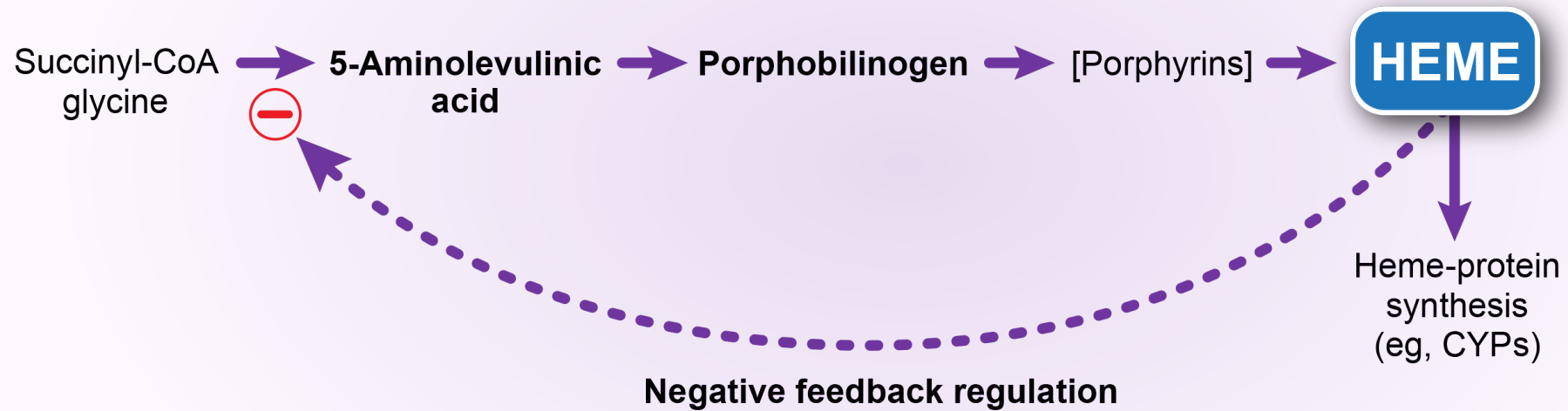
- AIP is 1 of 4 inherited types of acute porphyria
- AIP is responsible for most acute attacks that occur in the US and Europe
- Genetic testing defines the exact type (important for family screening)
- Management is the same for all types

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.

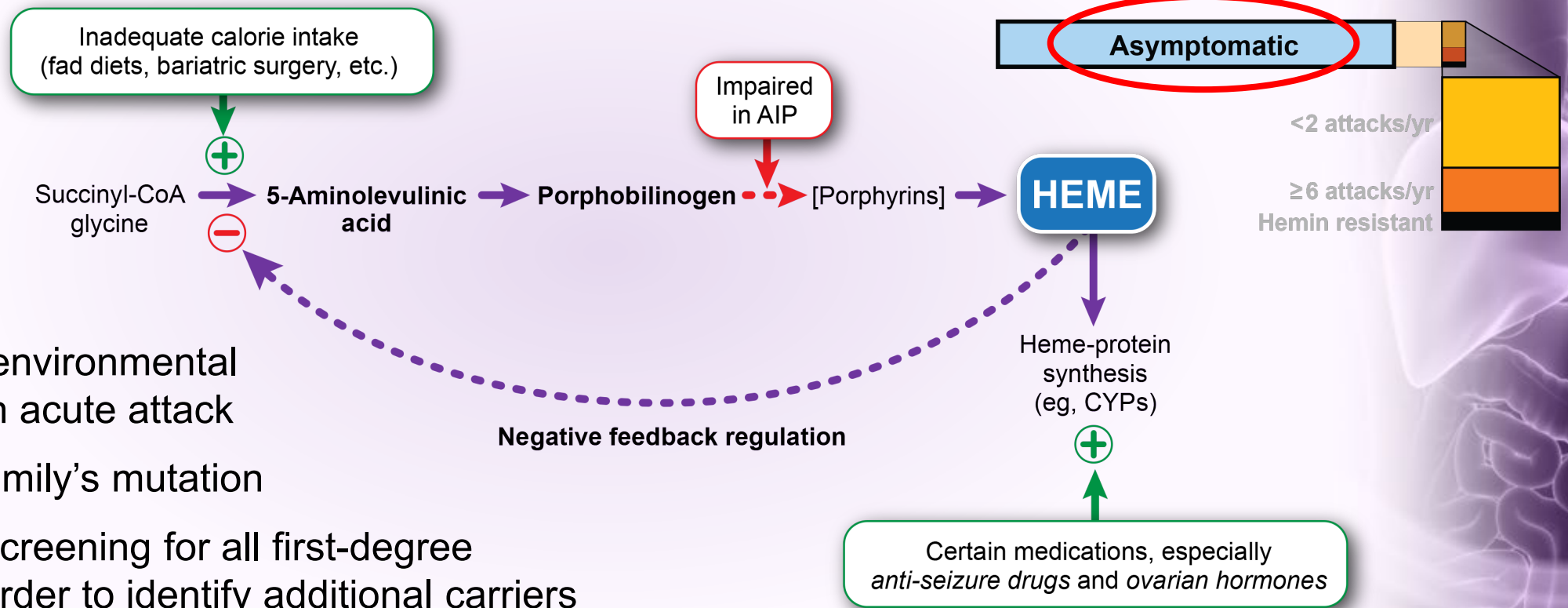
Management of AIP

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



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

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	



Treatment for Acute Attacks

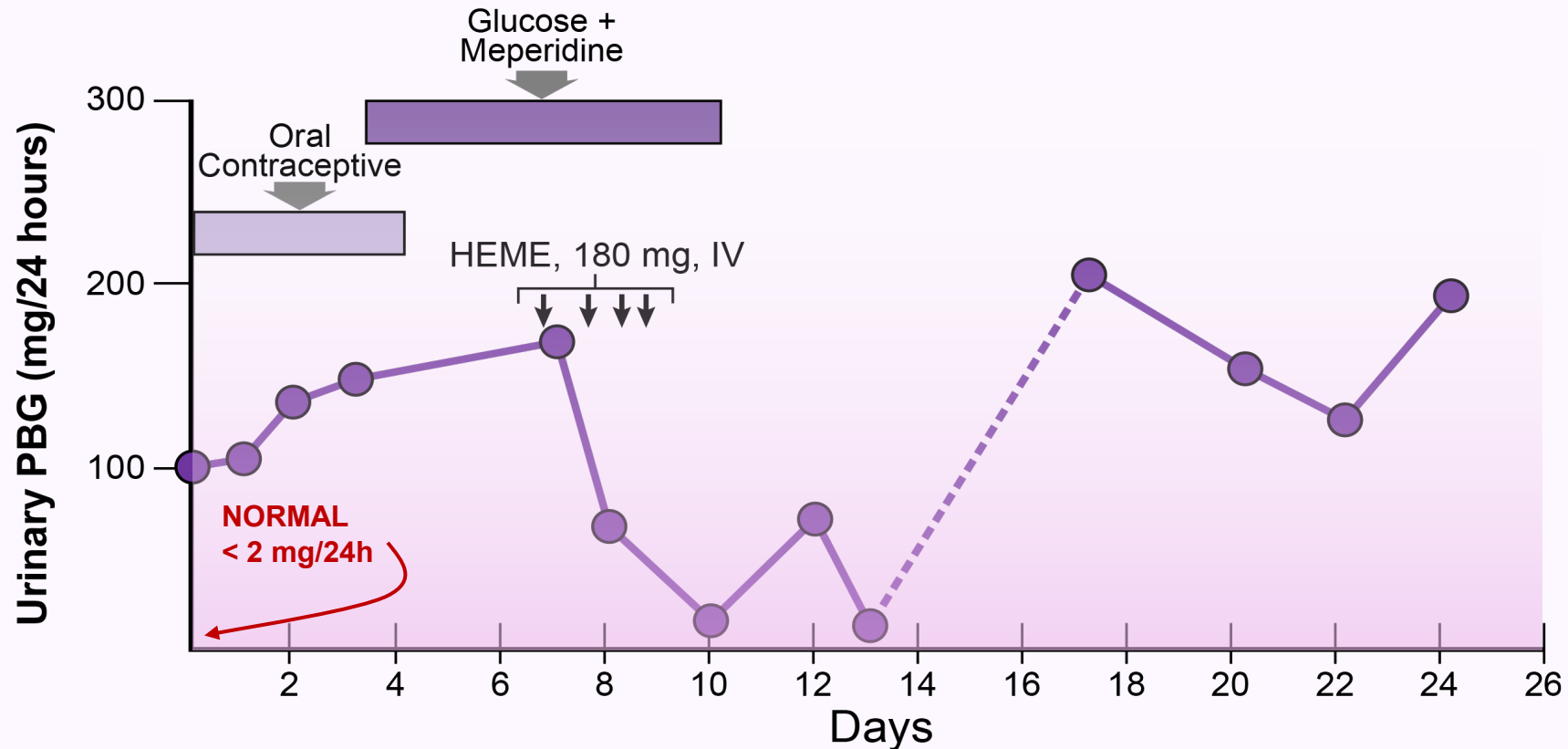
- Remove environmental triggers
- Provide fluid resuscitation (dextrose in saline) while watching for hyponatremia
- Relieve pain (with, eg, IV hydromorphone)
- Evaluate for other causes of nausea and abdominal pain
- Collect a urine sample to measure PBG and creatinine
- If the evaluation points to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



IV Hemin

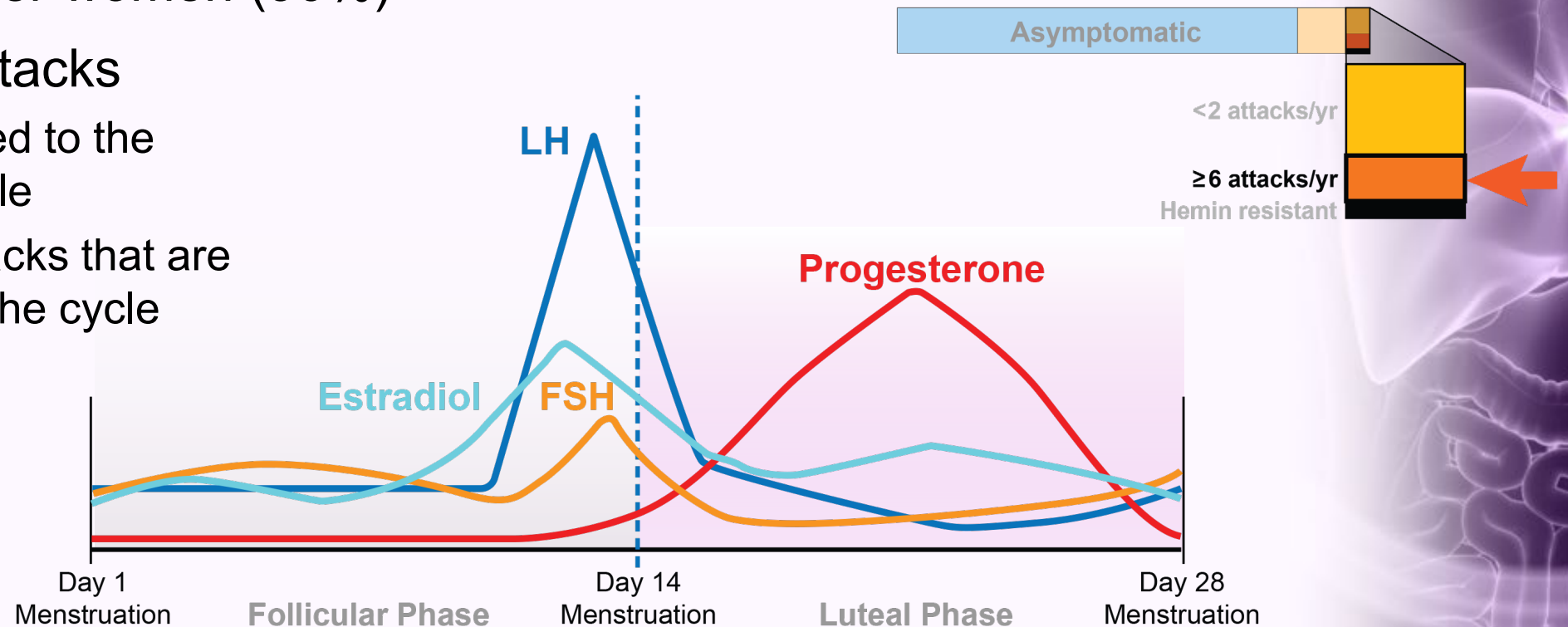
Biochemical Response to IV Hemin

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



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



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

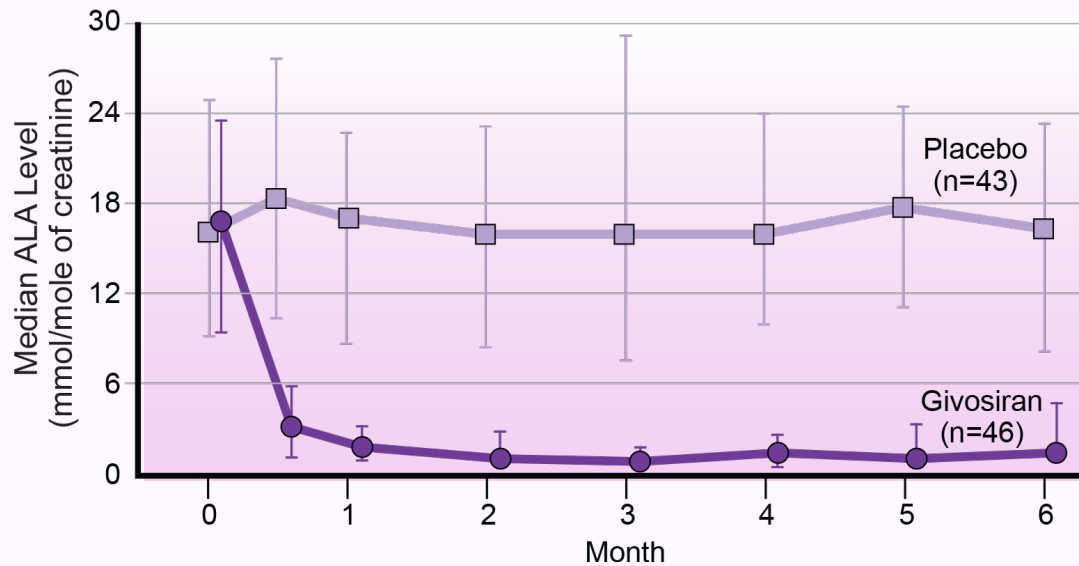


Givosiran

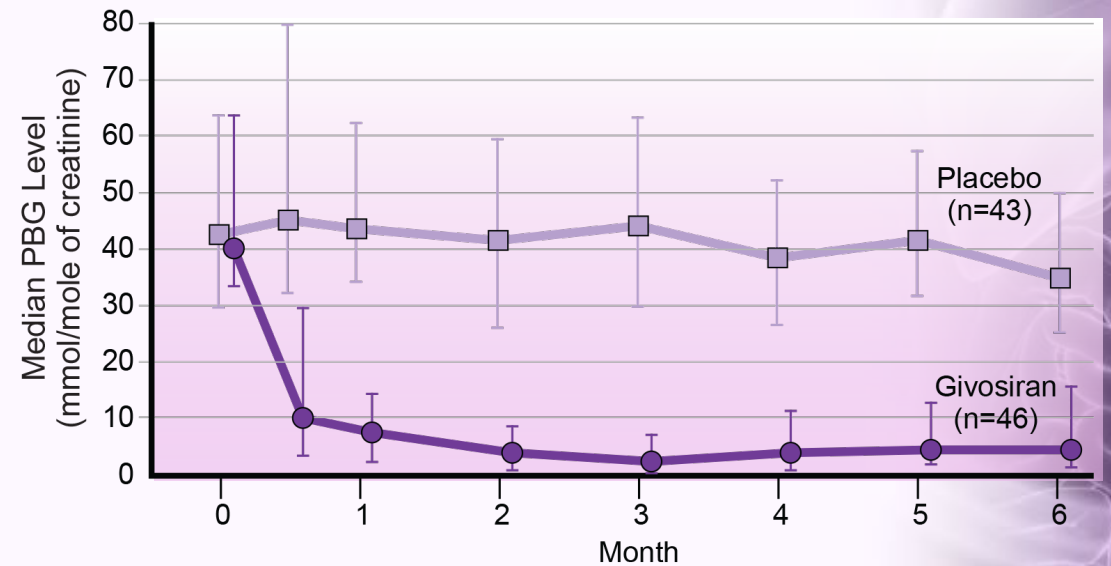
A new RNA-based drug that homes in on hepatocytes

- Causes ALA synthase mRNA to degrade and reduces ALA production

Urinary ALA Levels



Urinary PBG Levels



Givosiran (cont)

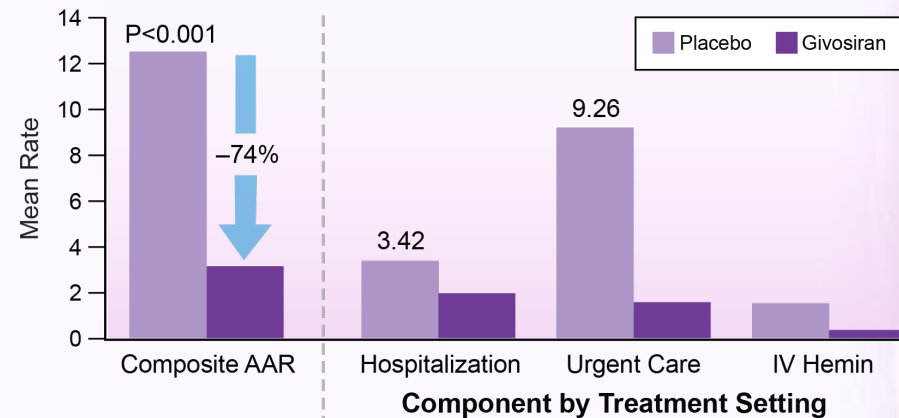
■ Positives

- Very effective at preventing acute flares of AIP
- SQ administration; no need for a visit to an infusion center
- A single injection provides a prolonged effect (at least 1 month)
- Side effects have been minor except for one reported case of anaphylaxis

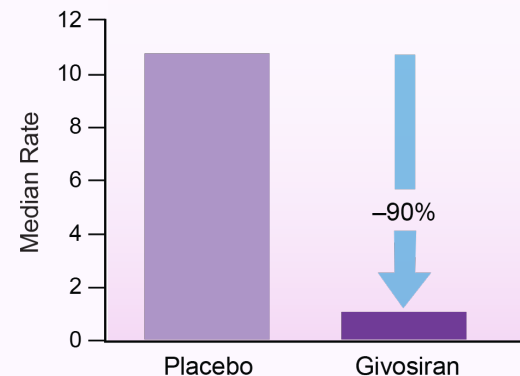
■ Negatives

- Not approved for use during pregnancy (data are lacking)
- Expensive (\$40,000 per injection)

Mean Annualized Attack Rate and Its Components

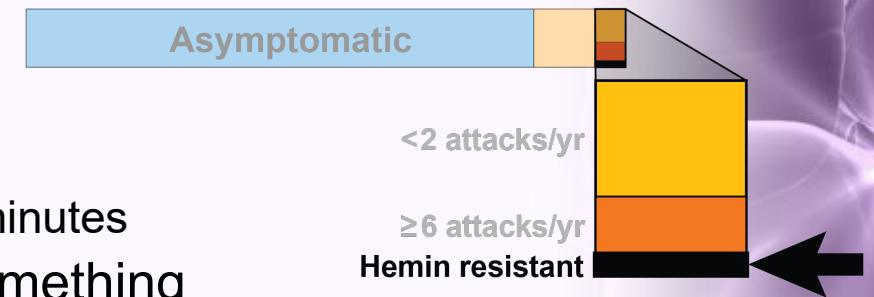


Median Annualized Attack Rate

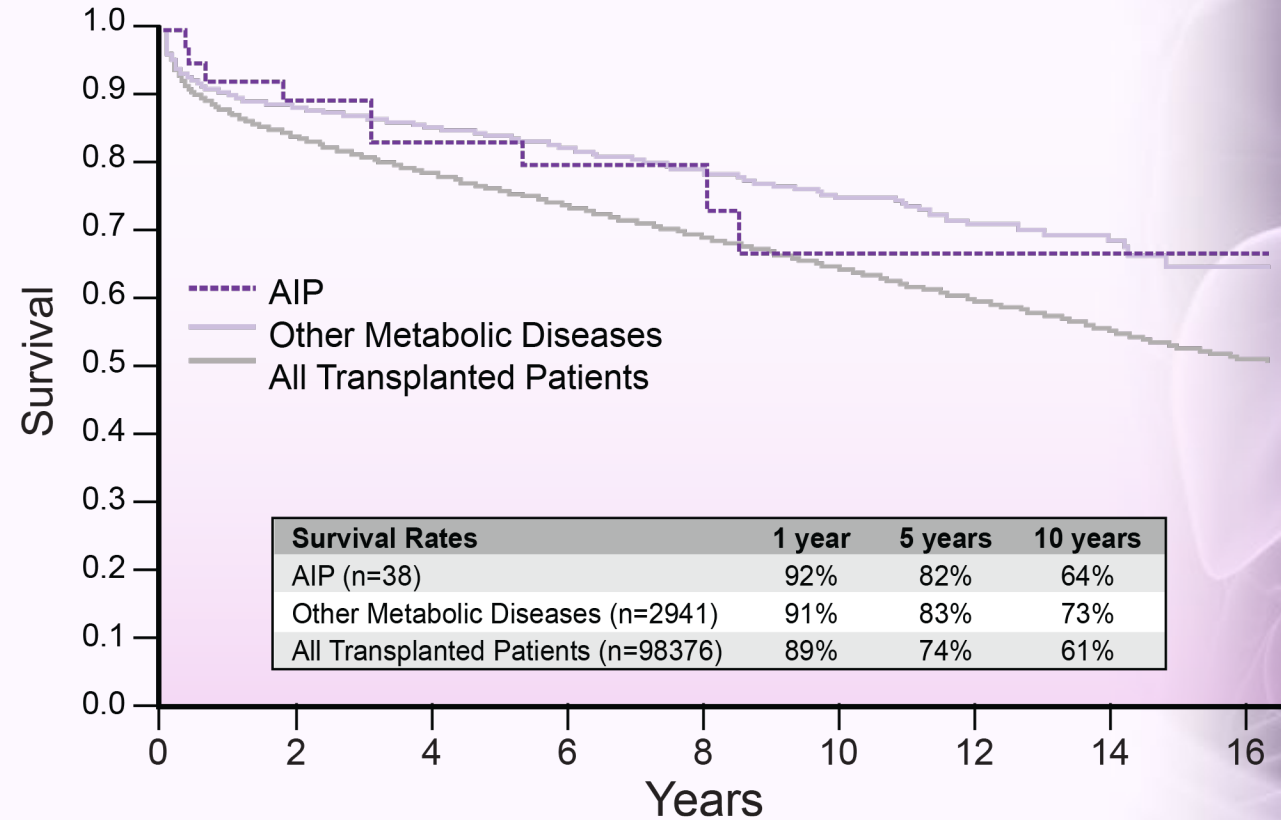
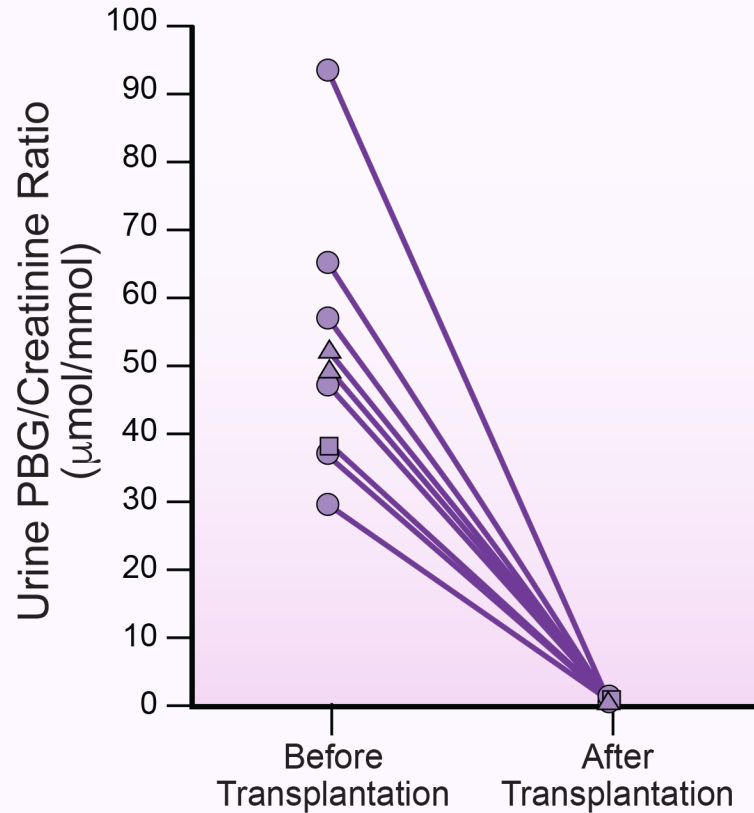


Hemin “Resistance”

- 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



Liver Transplantation for Acute Porphyria



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. Reproduced for educational purposes only.

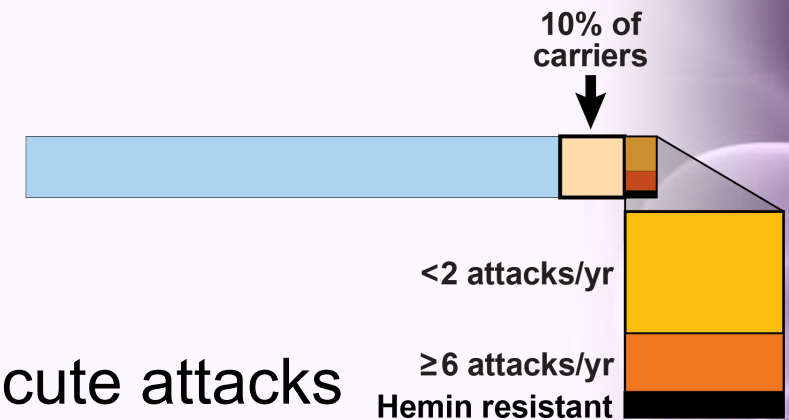
Challenges With Liver Transplant for AIP

- 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 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 carriers
- 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



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



Case: 23-Year-Old Woman Visits Her Gynecologist

- History of premenstrual pain and constipation; diagnosis of PMS
- Started taking an oral contraceptive 4 months ago for symptoms and initially noted some improvement
- During the past 2 weeks, pain and constipation have become worse
 - Now symptoms are accompanied by nausea, vomiting, and passage of “dark amber” urine
- Urine color suggests acute porphyria; urine was sent to test PBG
- 1 week later, PBG = 45 mg/g creatinine (normal value, <2 mg/g creatinine)
- Patient was diagnosed with AIP
- She continues to have ongoing nausea and pain but can keep fluids down



Question

What is the most appropriate next step in managing this patient?

- A. Prescribe a high-calorie diet and reassess in 1 week
- B. Discontinue oral contraceptives and reassess in 2 weeks
- C. Maintain close follow-up; if symptoms progress, send the patient to the emergency department for IV heme



Question

The oral contraceptive was discontinued. At follow-up, the nausea and pain have largely resolved, but her premenstrual pain continues. What is the most appropriate next step in managing this patient?

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



Question

At follow-up, the nausea and pain have largely resolved, but her premenstrual pain continues. What is the most appropriate next step in managing this patient?

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

Correct answer = A. GnRH analog



Question

Several months pass and the patient is doing fairly well. She would like something for birth control. What would you recommend?

- A. A low-dose oral contraceptive
- B. An etonogestrel implant
- C. A copper IUD
- D. A vaginal ring
- E. Medroxyprogesterone acetate



Question

Several months pass and the patient is doing fairly well. She would like something for birth control. What would you recommend?

- A. A low-dose oral contraceptive
- B. An etonogestrel implant
- C. A copper IUD
- D. A vaginal ring
- E. Medroxyprogesterone acetate

Correct answer: C. A copper IUD



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



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
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- 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



Interdisciplinary Care of AHP

- Acute porphyria is a multisystem disease that requires 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



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)

