

An Analysis of Healthcare Utilization and Costs Associated with Patients with Acute Hepatic Porphyrrias (AHP) with Recurrent Attacks in EXPLORE: A Prospective, Multinational Natural History Study of Patients with AHP

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Background and Rationale

Acute Hepatic Porphyrrias (AHP)

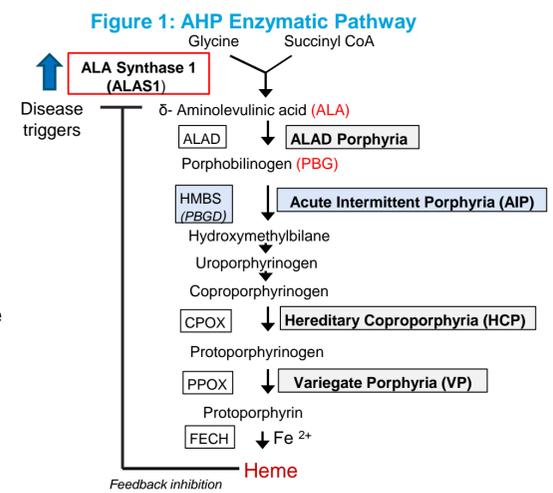
- Rare, serious, life-threatening metabolic disorder caused by a genetic mutation in heme biosynthesis, leads to accumulation of toxic heme intermediates porphobilinogen (PBG) and 5-aminolevulinic acid (ALA)¹⁻⁴ (Figure 1)
 - Includes acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP)
 - Characterized by occurrence of both acute disabling neurovisceral attacks, requiring hospitalizations (mean length of stay 5-7 days), and chronic debilitating disease symptoms impacting patients' daily functioning and quality of life²⁻⁴

Healthcare Utilization and Expenditure in AHP

- Given nature of attacks and chronic nature of disease it is important to understand healthcare utilization and expenditures associated with AHP to understand burden on healthcare system
- EXPLORE (NCT02240784)⁵ study is the first observational, multinational, prospective, ongoing study designed to characterize natural history and clinical management of patients with AHP where data are collected on health care utilization

Objective

- Estimate healthcare resource utilization and expenditures associated with treatment of patients with AHP who experience recurrent attacks (>3 attacks/year) or who receive prophylaxis to prevent attacks from perspective of US payer



Methods

- Healthcare resource utilization data from EXPLORE (Figure 2) and unit costs of resources (charges and economic costs) from publicly available sources (Table 1) were used to estimate annual expenditure per patient (Figure 3); both hospital charges (amount billed) and costs (amount paid) were reported. This analysis does not include indirect costs such as cost due to missed days of work, and caregiver costs.

Figure 2: EXPLORE Study Design



*Attacks defined as acute porphyria symptoms requiring increase in treatment (hemin, pain medications, carbohydrates) or hospitalization

- EXPLORE analysis included data for hospitalizations (including length of stay), ER visits, and GP/Specialist visits
 - Patients asked at baseline about healthcare utilization over past 12 months
- Frequency of hemin prophylaxis use was filled out by health care provider and obtained from current medication log
- Attack rate and duration during study period calculated
 - Use of hemin to manage attacks estimated based on expert opinion depending on duration of attack
- Probabilistic sensitivity analysis (PSA) conducted to quantify uncertainty in model estimates
 - Uncertainty in annual resource utilization inputs obtained from EXPLORE was quantified in terms of mean and standard errors
 - Standard errors calculated from reported standard deviation and study sample size or otherwise calculated from data

Results

Patient and Disease Characteristics

- 112 patients (mean 39.3 years, 89% female, 85% white/Caucasian) enrolled from 13 countries (US: 44%; EU (12 countries): 56%)
 - AHP subtype: 93% AIP, 3% HCP, and 4% VP
 - Follow-up: 107 (96%) and 80 (71%) patients completed 6 and 12 months, respectively
- Commonly associated medical conditions included renal/vascular disorders (38%), nervous system disorders (31%), psychiatric/sleep disorders (30%), and gastrointestinal disorders (22%)
- Patients reported annualized attack rate of 4.9 with average duration of 7 days. Patients with hemin prophylaxis had annualized attack rate of 4.1 and those without prophylaxis had an attack rate of 5.5

Healthcare Utilization Rates

- Patients reported frequent health care utilization use with an average of 4.5 hospitalizations lasting an average of 6.6 days (Table 2)

Table 2: Patient-Reported Porphyria-Related Healthcare Utilization in Past Year*

Healthcare Utilization Category	Result
PCP Visits	
Monthly or more frequent, n (%)	27 (24)
Every 2-12 months, n (%)	40 (36)
Specialist Visits	
Monthly or more frequent, n (%)	40 (36)
Every 2-12 months, n (%)	60 (54)
Emergency department visits, mean [SEM] (range)	2.8 [4.2] (0-20)
Overnight hospitalizations, mean [SEM] (range)	4.5 [0.89] (0-70)
Duration of hospital stay, days, mean [SEM] (range)**	6.6 [1.0] (1-60)
Patients with hemin prophylaxis (%)	46.4%

SEM, Standard error of the mean* Patients were asked at baseline about their healthcare utilization in past 12 months; ** Total hospitalization days is approximated by product of number of times the patient stayed overnight in the hospital in past 12 months and average duration of hospital stay up to 4 hospitalizations for that patient

Summary

- Healthcare utilization and expenditures for management of patients with AHP was high, driven by hospitalizations and hemin use, both for attacks and prophylactically
- Estimated average annual expenditure/patient was \$398,463 (95% CI: \$328,303 - \$475,477) to \$655,418 (95% CI: \$482,278 - \$847,448) depending on whether hospital costs or charges were used
- Limitations included:
 - Annual expenditure/patient is presented as both hospital cost and charge; charge may overestimate annual expenditure/patient and cost may underestimate annual expenditure/patient
 - ICD-9 code is not specific to porphyrias; thus hospitalization costs may be under-represented due to disease severity; both costs and charges are presented
 - Indirect costs and other treatment costs (e.g., treating disease complications and adverse events) were not captured
 - Variability of patient's clinical presentation results in differences in costs and utilization, thus a PSA was conducted to account for uncertainty around sample mean
 - Use of hemin was based on one expert's opinion and future studies should look at actual use of hemin
- Treatment options that reduce attacks and thereby hospitalizations may result in lower economic burden on US health care system
- This is the first study to estimate expenditures associated with management of AHP and represents a significant burden to US healthcare system; future studies should evaluate expenditures from claims databases and expenditures associated with management of AHP in other countries

Disclosures: Amy Chan, Chang-Heek Soh, Kirsten McCarthy, William Querbes, Craig Penz, Sonalee Agarwal, and Amy Simon are employees of Amylin Pharmaceuticals. References: 1. Puy, H., et al., Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria. Am J Hum Genet. 1997; 60(6): p. 1373-83; 2. Pischik, E. and R. Kauppinen, An update of clinical management of acute intermittent porphyria. Appl Clin Genet. 2015; 8: p. 201-14; 3. Anderson, K.E., et al., Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med. 2005; 142(6): p. 439-50; 4. Naik, H, Stoeker, M, Sanderson, SC, Balwani, M, Desnick, RJ. Experiences and concerns of patients with recurrent attacks of acute hepatic porphyria: A qualitative study. Mol Genet Metab. 2016;119(3):278-283; 5. Anderson, K., EXPLORE: A prospective, multinational natural history study of acute hepatic porphyria patients with recurrent attacks. Hepatology 2016; 64[S1]. (Poster presentation).

Figure 3: Model to Estimate Annual Expenditure per Patient

PCP Visit Utilization	×	PCP Visit Unit Cost	=	PCP Visit Annual Cost
Specialist Visit Utilization	×	Specialist Visit Unit Cost	=	Specialist Visit Annual Cost
ER Visit Utilization	×	ER Visit Unit Cost	=	ER Visit Annual Cost
Hospitalization Utilization ^a	×	Hospitalization Unit Cost	=	Hospitalization Annual Cost
Hemin Prophylaxis Utilization	×	Hemin Prophylaxis Unit Cost	=	Hemin Prophylaxis Annual Cost
Hemin Acute Utilization based on Expert Opinion ^b	×	Hemin Acute Unit Cost	=	Hemin Acute Annual Cost
Hemin Administration Utilization	×	Hemin Administration Unit Cost	=	Hemin Administration Annual Cost
				=
				Total Annual Cost per Patient

^aHospitalization utilization is average overnight hospitalization × average length of stay; ^bHemin acute utilization is annualized attack rate × 4 vials of hemin
Source: Expert opinion based on average duration of attack

Table 1: Cost Inputs from Published Data Sources in the US

Resource	Cost	
	Uninflated (year)	Inflated
PCP visits (CPT 99213) ^{a,b}	\$73.93 (2017)	\$73.93
Specialist visits (CPT 99214) ^{a,b}	\$108.74 (2017)	\$108.74
ER visits ^c	\$1,097 (2010)	\$1,340
Hospitalization		
Cost per day ^{d,e}	\$3,091 (2014)	\$3,370
Charge per day ^{d,e}	\$11,021 (2014)	\$12,015
Hemin vial ^f	\$7,231.55 (2017)	\$7,231.55
CVAD (CPT 36561) ^{g,h}	\$1,625.71 (2017)	\$1,625.71
PICC (CPT 36569) ^{g,h}	\$254.74 (2017)	\$254.74
IV infusion (CPT 96365) ^{a,b}	\$69.98 (2017)	\$69.98

GP, general practitioner; CPT, current procedural terminology; ER, emergency room; CVAD, central venous access device; PICC, peripherally inserted central catheter; IV, intravenous; Sources of information: ^aCenters for Medicare and Medicaid Services; ^bPhysician Fee Schedule; ^cNational Center for Health Statistics (2012); ^dAgency for Healthcare Research and Quality; ^eHealthcare Utilization Project; ^fRed Book, Pathemstem costs er visit; ^gCook Medical; ^hCoding and Reimbursement Guide

Costs

- Overall expenditures associated with management of AHP are high, with the greatest costs associated with hospitalizations and hemin use both for management of attacks as well as prophylaxis use (Table 3)
 - Average annual expenditure based on hospital cost estimates per patient is about \$398,463 (\$328,303 - \$475,477) while those based on hospital charge estimates are \$655,418 (\$482,278 - \$847,448)

Table 3: Annual Healthcare Expenditure per Patient by Utilization Category

Healthcare Utilization Category	Average Annual Cost Per Patient
PCP Visits	\$443
Specialist Visits	\$1,203
ER Visits	\$3,753
Hospitalizations	
Costs	\$100,078
Charges	\$356,853
Hemin Prophylaxis	\$148,145
Hemin Acute Attacks	\$141,738
Hemin Administration	\$3,282
Total with Hospital Costs, mean (95% CI)	\$398,463 (\$328,303 - \$475,477)
Total with Hospital Charges, mean (95% CI)	\$655,418 (\$482,278 - \$847,448)

PCP, Primary Care Physician; ER, emergency room
*Categorical data for PCP and specialist office visits were converted to mean annual visits by multiplying the frequency of response by the number of annual visits (e.g., monthly visits were represented as 12 annual visits) and the average for the entire sample was estimated.
Hemin prophylaxis utilization at baseline was also converted from categorical response to mean annual infusions per patient by multiplying the frequency of response by the number of annual infusions for the entire response set.
Treatment days with hemin per attack were based on expert opinion from Dr Balwani, who reports that the average attack is treated for 4 days. It was assumed that 50% of prophylaxis patients receive their infusions in the office. For acute attacks, it was estimated that 65% of AHP patients and 70% of AIP patients receive infusions in the office (based on the ratio of attacks treated in a health care facility to all on-study attacks)