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Benefits of prophylactic heme therapy in severe acute intermittent porphyria

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ABSTRACT

Acute intermittent porphyria (AIP), an autosomal dominant inborn error of metabolism, is the most common and severe form of the acute porphyrias. Attacks of severe abdominal pain, often with hypertension, tachycardia, are cardinal features of AIP, often requiring hospital admissions. Frequent recurrent attacks of AIP, defined as > 3 attacks in one year, during which at least one attack requires intravenous heme therapy, are associated with significant morbidity, lost productivity, and health care burden. We report two patients with such frequent attacks of AIP, who have been managed with prophylactic heme therapy on a weekly basis. We describe results particularly in relation to symptom control, biochemical findings, health care costs, quality of life, and utilization of resources. During 11-month duration of weekly prophylactic heme infusions, we observed a 100% decrease in acute attacks and inpatient admissions in one subject and a 75% decrease in the other. During this time, we also observed a significant decrease in the number of emergency room visits. The decrease in number of acute attacks requiring hospital admission was associated with significantly decreased health care costs and improved quality of life. Reduction of both emergency room visits and hospital admissions decreased the utilization of health care services. Outpatient weekly infusions were also noted to be associated with better reimbursements and reduced overall costs of health care for the subjects. Both our subjects also endorsed better symptom control, quality of life and better understanding of disease. Thus, prophylactic heme therapy, through a multi-disciplinary approach, decreases the incidence of acute attacks, decreases health care costs and leads to better patient satisfaction and quality of life.

1. Introduction

Porphyrias are a group of eight metabolic disorders, mainly inherited inborn errors of metabolism, characterized by defects in heme biosynthesis. They are inherited in an autosomal dominant or recessive fashion. Acute hepatic porphyrias (AHPs) include three dominantly inherited disorders, namely, acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), as well as a rare autosomal recessive disorder, 5-aminolevulinic acid (ALA) dehydratase deficiency porphyria [1,2]. AIP is due to mutations in the hydroxymethylbilane synthase (*HMBS*) gene, also known as porphobilinogen deaminase, which results in decreased enzymatic activity, in this the third enzyme in heme biosynthetic pathway [1–3]. AIP presents as acute attacks of pain, usually in the abdomen often accompanied by sympathetic nervous system over-activity [systemic arterial hypertension, tachycardia, sweating], hyponatremia, sometimes with other neurologic manifestations such as weakness, delirium and seizures [4–6]. Acute porphyric attacks typically start after puberty and can be triggered by exogenous factors such as medications, stress, exogenous hormones, nutritional status and infection, although for many patients, no triggering factors are identified [8]. Measurements of urinary porphobilinogen (PBG) and ALA, which are elevated, continue to be the primary means of initial diagnosis of acute porphyric attacks [6,8]. Urinary ALA levels during acute attacks are elevated ~5–20 times and, except in the very rare autosomal recessive ALADP porphyria, PBG is even more elevated ~10–50 times the upper limit of normal [8]. Treatment of acute attacks involves removal of precipitating factors (eg, severe dieting/caloric restriction or medications), as well as carbohydrate loading, often administered as intravenous dextrose, in order to down-regulate hepatic ALA synthase 1, the first and normally rate-controlling enzyme of the pathway, which is known to be down-regulated by high glucose loads or other metabolizable carbohydrates [the so called 'glucose effect'] [10]. Carbohydrate loading may be an effective treatment in patients with mild and uncomplicated attacks.

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However, the treatment of first choice for all but mild acute attacks is IV heme therapy. IV heme was the first Orphan Drug approved for use in the USA. Currently, it is available as Panhematin® (lyophilised hematin [hydroxyheme], Recordati Rare Chemicals) in the United States and as Normosang® (heme arginate, also from Recordati) in the European Union. These agents are available in some other countries, as well. Symptomatic therapy along with infusions of intravenous heme therapy and generous administration of carbohydrates [~300 g/d of dextrose or similar] form the cornerstone of treatment of acute porphyric attacks. A typical regimen for heme therapy is four days, which usually are sufficient for significant clinical improvement and decrease in PBG levels [6,9]. Attacks typically last no longer than 1–2 weeks, but they can be life-threatening with a mortality rate of up to 10% if not diagnosed promptly and treated appropriately [8,9]. Most moderate or severe acute attacks require hospital admission and close monitoring for potential complications that chiefly include severe systemic arterial hypertension, tachycardia, sometimes with life-threatening cardiac arrhythmias, hyponatremia, delirium, seizures, and progressive motor weakness. Of course, in-patient care is associated with higher costs when compared to out-patient management. In this report, we summarize clinical courses and laboratory features of two patients with AIP, with frequent recurrent attacks that required repeated hospital admissions prior to their beginning weekly, prophylactic infusions of IV Panhematin. They experienced improved symptom control and quality of life, and there were appreciable decreases in health care utilization rates and costs after institution of weekly prophylactic infusions of Panhematin.

2. Methods

We enrolled these subjects in a prospective observational study for longitudinal study of the natural history of AIP with recurrent attacks. Detailed history, previous medical visits and treatments had been obtained prior to enrollment. Frequent recurrent attacks were defined as at least 3 acute porphyric attacks requiring treatment in the 12 months prior to baseline visit with at least one attack requiring hematin or treatment at hospital or clinic.

Subjects were educated and counseled about weekly Panhematin infusions as prophylaxis to try to prevent frequent recurrent attacks. The subjects consented to participate in the study and were followed over the ensuing 11-month period. Subjects were given IV hemin as Panhematin, 4-mg/kg body weight, infused intravenously once every week. Hemin (Panhematin) is available in the United States as lyophilized hydroxyheme (hematin) for reconstitution and is approved by FDA for ameliorating acute porphyric attacks [6]. Reconstitution was done with human albumin to enhance stability and to decrease adverse effects, such as thrombophlebitis and phlebosclerosis [7]. Subjects also received one-liter bolus of 5% dextrose + ½ normal saline along with as needed heparin flushes and anti-nausea medications.

3. Clinical vignettes

3.1. Case 1

A 22-year-old Caucasian woman with previous medical history of renal calculi presented with generalized abdominal pain for 2–3 days during the initial evaluation. Pain was associated with recurrent episodes of non-bilious, non-bloody vomiting, anorexia and inability to eat, and passage of dark reddish-brown colored urine. She described abdominal pain as upper (both epigastric, RUQ and LUQ along lower rib cage), with severity 10/10 at onset, radiating to the back, sharp and constant in nature. She also gave a history of alternating diarrhea and constipation. Prior to her initial presentation at our Center, she had required multiple admissions to outside hospitals every 3 to 4 weeks for undiagnosed abdominal pain for > 2 years. She was an active smoker of cigarettes [~1 pack per day]; she denied alcohol use. Comprehensive metabolic panel, CBC, and urinalysis were normal; an acute hepatitis panel [for hepatitis A, B, and C] was negative. She had been evaluated extensively with colonoscopy, upper GI endoscopy and CT and ultrasound studies of the abdomen and pelvis, all with normal findings, which had provided no explanation for her severe and recurrent episodes of pain. She had been found to have renal calculi, which had been removed without benefit of decreased frequency or severity of symptoms. She also had undergone cholecystectomy; there were no gall stones and no evidence of bile duct abnormalities, and her pain continued. Other than worse symptoms during the luteal phase of her menstrual cycle, there were no identifiable precipitating causes for her recurrent severe pain. In the years before her initial visit at our Center, she had also been suggested perhaps to have idiopathic gastroparesis, but gastric emptying studies had been normal. Family history was unremarkable, except that her mother had similar symptoms on and off for many years with no clear diagnosis having been made. The patient has three siblings who were reported to be asymptomatic and who declined any evaluation.

During her initial visit to our Center, we considered the possibility that she might have an acute hepatic porphyria [AHP]. Initial evaluation showed normal urinary delta- aminolevulinic acid (ALA) level of 5.9 mg/g creatinine [ref range 0–7]. Urinary porphobilinogen (PBG) was modestly elevated at 10.3 mg/g creatinine [ref 0–4]. Total urinary porphyrins were 284 nmol/g creatinine [ref 0–300]. Erythrocyte HMBS [aka PBGD] activity was decreased at 11 nmol uroporphyrin/mL RBC/h [ref range 20–50]. These results indicated that the patient has AIP. Fecal and plasma total porphyrins were normal, providing evidence against variegate or hereditary coproporphyria. Genetic testing showed that she has the missense mutation of c.992C > T, corresponding to p. A331V in one of her *HMBS* alleles. This is a previously described disease-causing mutation associated with AIP.

After the young woman had returned monthly for 6 months, each time with recurrent acute attacks that required hospitalizations, we convinced her to have a central venous port placed and by this means to receive a trial of weekly prophylactic IV heme in the form of Panhematin. We recommended smoking cessation and offered counseling sessions, which she refused. We also discussed hormonal therapies during these 6 months. The patient refused any such therapies because she wanted to conceive.

3.2. Case 2

A 59-year-old Caucasian man with known past medical history of AIP, and systemic arterial hypertension had required at least monthly hospital admissions to an outside hospital, each of 6–7 days' duration for management of acute attacks over a period of several years. He also had uncontrolled systemic arterial hypertension [typical BP 230/130 mmHg] along with dehydration during these attacks. The patient was already known to carry an *HMBS* c.713 T > C, p. L238P mutation, a mutation known to be associated with active AIP. Typical monthly attacks included severe abdominal pain, back pain, nausea and anorexia, which required repeated emergency room visits and monthly inpatient admissions. He also had undergone cholecystectomy for chronic abdominal pain, without benefit. There were no clear precipitating factors or causes for most of his recurrent attacks. The family history is that his brother has similar symptoms, but he has refused full evaluation. The patient had been married, but he was divorced when he first presented to us; he had no children. He was an active smoker of cigarettes but denied alcohol consumption.

He typically had markedly elevated urinary PBG (usually 60–100 mg/g creatinine), ALA (usually 50 to 100 mg/g creatinine), and elevated total porphyrins (usually 1300–2500 nmol/g creatinine, with 60–85% uroporphyrin and most of the rest coproporphyrin). During his inpatient admissions, he required aggressive hydration with dextrose, large doses of intravenous narcotic analgesics and anti-nausea medications [ondansetron, promethazine] for symptomatic control.

Typically, he was dehydrated during the attacks because of nausea and vomiting and poor intake of fluids during and prior to attacks. During acute attacks, he also was treated with intravenous Panhematin reconstituted in albumin at a dose of 4 mg/kg BW daily. He typically required five days of therapy prior to discharge. He responded well after 4 days of IV Panhematin with urinary PBG levels decreasing to ~9 mg/g of creatinine. He also had elevated serum ferritin levels, typically > 2000 ng/mL [ref 30–282], likely secondary to many years of Panhematin infusions, which had led to secondary iron overload. On initial presentation at our Center, comprehensive metabolic panel and complete blood count were normal. Serum alpha-fetoprotein and hepatitis panel were normal/negative. He had MRI of the liver done which did not show any tumor. We repeatedly recommended smoking cessation, but the patient continued to smoke and did not participate in counseling sessions.

After he had returned monthly for 12 months, requiring hospital admissions of 5–7 days out of every 30 days, we convinced the patient to again have a central venous port inserted [a prior one had become non-functional, and the patient had heretofore refused replacement] and thereby to undertake a trial of weekly prophylactic IV Panhematin.

4. Results

4.1. Utilization of health care resources and total costs of recurrent hospital admissions vs prophylactic outpatient infusions of Panhematin

In a total of 11 months' follow-up for both the subjects after they had instituted weekly prophylactic Panhematin, we observed markedly decreased numbers of emergency room visits and inpatient admissions for acute porphyric attacks. Specifically, patient 1 had required nearly monthly admissions during the one year prior to institution of weekly prophylactic Panhematin (11 inpatient admissions over 12 months). After initiating weekly prophylactic Panhematin, she required no further inpatient admissions and tolerated infusions well. She had only one emergency room visit [for nausea] during this prophylactic Panhematin period. On that occasion, she did not require hospital admission but was managed in the emergency department and improved.

Patient 2 had, for several years, required hospital admissions at least monthly. For example, in the year just prior to the institution of weekly prophylactic Panhematin, he had required 13 inpatient admissions over 12 months. After weekly prophylaxis had been instituted, he required only three visits to the ED and admissions during an 11-month follow-up.

Patient 1

Follow up time period (11 months)	Before weekly infusions (Observed time = one year)	During weekly infusions
No. of admissions	11	Zero
No. of ED visits	13	One (Discharged from ED)

Patient 2

Follow up time period (11 months)	Before weekly infusions (Observed time = one year)	During weekly infusions
No. of admissions	13	3
No. of ED visits	18	3 (Admitted from ED)

4.2. Biochemical findings during acute exacerbations and during weekly prophylactic Panhematin infusions

See Tables 1–4.

Table 1
Patient 1 Urinary levels of ALA (0–7 mg/24 h) and PBG (0–4 mg/24 h) during inpatient admission, during which she received daily IV Panhematin for four consecutive days.

Urinary excretions	Day 1	Day 2	Day 3	Day 4
Urine ALA (mg/g creatinine)	5.0	3.8	1.6	2.0
Urine PBG (mg/g creatinine)	8.2	5.0	1.7	1.5

First void morning urines obtained on each day, prior to IV Panhematin infusions.

Table 2
Patient 1 during weekly infusions (Consecutive weeks).

Urinary excretions	Week 6	Week 7	Week 8	Week 9
Urine ALA (mg/g creatinine)	13.6	6.4	7.1	9.6
Urine PBG (mg/g creatinine)	24.5	8.6	13.1	17.2

First void morning urines obtained, prior to IV Panhematin infusions.

Table 3
Patient 2 Urinary levels of ALA and PBG during inpatient admission, during which he received daily IV Panhematin for four consecutive days.

Urinary excretions	Day 1	Day 2	Day 3	Day 4
Urine ALA (mg/g creatinine)	50.1	9.4	7.7	4.9
Urine PBG (mg/g creatinine)	86.5	20.5	15.7	9.4

First void morning urines obtained on each day, prior to IV Panhematin infusions.

Table 4
Patient 2 Urinary ALA and PBG just prior to weekly prophylactic infusions of Panhematin (consecutive weeks).

Urinary excretions	Week A	Week B	Week C	Week D
Urine ALA (mg/g creatinine)	52.7	74.5	41.1	62.8
Urine PBG (mg/g creatinine)	95.9	106.2	65.9	100.2

First void morning urines obtained prior to IV Panhematin infusions.

4.3. Costs of health care delivery

Costs are described in relation to costs attributed to the hospital for providing the care. Direct cost is defined as cost attributable directly to patient care, and includes medication costs. Total cost is defined as complete cost of care, which includes all indirect costs in addition to direct costs. Heme 'direct cost' is the cost of infusing heme during the visit to hospital. All the information provided is attributed to the hospital charges or costs, and this does not reflect any patient responsibility. [Direct reimbursements to the hospitals for the care provided by insurance providers cannot be provided here due to data privacy and security provisions under Health Insurance Portability and Accountability Act of 1996 (HIPAA)]. Hospital costs vary with length of stay and level of care based on patients' clinical conditions (Tables 5 and 6).

Table 5
Shows comparison costs between each inpatient visit (average length of stay [LOS] = 5 days) and each outpatient visit.

Patient 2	Inpatient (LOS = 5 days)	Outpatient visit (1 visit)
Average Direct cost	$46,690	$7470
Average Total cost	$65,208	$10,087
Heme Direct Cost	$29,920	$5051

Costs for Patient 2—Average Costs–Inpatient vs Outpatient/episode.

Table 6
Shows comparative costs for Patient 2 over a one-year period. Average costs over one year include 12 inpatient admissions and 56 outpatient visits, described a frequency (n). All charges have been rounded to nearest dollar and all percentages (%) to nearest whole number. Described below is the percentage reduction in costs without taking reimbursements into consideration.

Patient 2	Inpatient (n = 12)	Outpatient (n = 56)	% Reduction in cost
Average direct costs	$560,280	$331,104	25%
Average total costs	$782,484	$448,428	29%
Heme direct costs	$359,040	$206,784	21%

Costs for Patient 2—Average Costs–Inpatient vs Outpatient/year.

As shown above, annual costs decreased by about 25% for weekly prophylactic outpatient infusions when compared to frequent inpatient admissions.

Note also that the direct costs of heme account for 63% of the average direct cost and 46% of average total cost for the health care system.

4.4. Symptom control and quality of life

Both subjects showed notable improvement with symptom control with decreased acute exacerbations over 11 months follow up. Pain, nausea, vomiting and self-perception of symptoms have shown consistent improvement on follow-up visits. In our subjects, patient 2 was dependent on opioids, and likely subjective perception of pain was higher when compared to patient 1. Quality of life also improved with weekly infusions when compared to previous monthly 5–7 day admissions. Patient 2 expressed improved tolerance of pain, lesser severity of symptoms, better satisfaction and well-being in general. For example, for the first time in over a decade, during which he had spent 5–7 days of every month in the hospital, he was able again to pursue his passion for photography and to travel. Patient 1 also expressed that weekly infusions helped her carry on with her daily activities and improved quality of life. For example, she reported that she did not require missing work because of symptoms and was again able to take regular exercise. Based on studies done before from databases, in relation to acute medical conditions, an improved patient satisfaction was noted in observation units (typical to our setting of out-patient infusions) when compared to inpatient management [11].

5. Discussion

Frequent recurrent attacks of AIP, described, as > 3 per year requiring intravenous heme, constitute a debilitating disease state, with significant burden on health care systems and also markedly impaired quality of life. Hemin has been used prophylactically to prevent recurrent attacks that continue even after precipitating factors identified have been addressed [18]. For patients with frequent recurrent attacks, prophylactic infusions individualized to the patient severity may be beneficial, but specific guidelines for such therapy, the optimal frequency of prophylactic heme administration, or when to consider trial cessation of prophylactic therapy are not clearly defined. Even though such therapy has been suggested as 'on demand' or prophylactic infusions in an outpatient center, no further benefits were described [19]. We here report two patients with recurrent attacks of AIP, both of whom experienced marked improvements in overall health status and quality-of-life after they began prophylactic IV heme therapy. As noted, notable improvement in quality of life, and amelioration of symptoms were reported consistently with improved patient satisfaction on weekly hematin infusions. Both these subjects also endorsed better understanding of their disease pattern, recognition of prodromal symptoms and appreciated the improved accessibility to ongoing health care and avoidance of the need for repeated visits to the ED and hospital admissions. A better quality of life and self-perception of well-being was reported both on clinical visits and follow-up phone calls. In a similar vein, Marsden et al. described improvement in clinical symptoms, physical activity, and work attendance [18].

Also worthy of note is the significant decrease in health care burden and total costs due to the decrease in the incidence of acute attacks. A weekly scheduled prophylactic treatment regimen decreased the number of inpatient admissions significantly when compared to treating acute attacks. The weekly prophylactic regimen also decreased the number of emergency room visits, thereby improving the patient satisfaction and quality of life overall and reducing stress on an already over-burdened ED system. Following the institution of weekly heme infusions, other important benefits were an improved physician-patient relationship and confidence in each other, which are of paramount importance for better management of patients with chronic diseases such as AIP. As noted above, the decrease in health care utilization significantly reduced health care costs; lower medication costs and total costs, and better reimbursements are clearly associated with the outpatient prophylactic regimen.

Diagnosis and treatment of acute medical conditions form the largest share of total US health care costs (32.4% in 2014) [12]. A Significant increase in expenditures of about 4.1% was noted in 2014 when compared to 3.5% in 2013 for hospital-based care, which was attributed to greater use and intensity of services [11,12]. Based on 2012 data, mean hospital cost per medical admission, regardless of insurance payer, with inflation adjustment was $8500 [14]. The mean average cost per bed per one day of inpatient care in US, excluding costs of drugs and some other services, varies from $788.5 to $1093.5 dollars, based on the level of care [13]. In 2012, typical mean hospital costs were $12,200 for Medicare as primary payer, and $9700 for private insurance as primary payer [14]. In our AIP patients, an estimated 4 to 5-day inpatient stay is required for management of an acute attack.

In general, costs of in-patient care are significantly higher than outpatient based infusions, primarily because of cost of stay in hospital, costs for utilization of resources and also medication costs. Currently, in the USA, reimbursements for hospitals or clinics in relation to medication costs specifically for infusions are generally higher for outpatients than for inpatients. Based on the results above, in our patients, appreciable health care savings were noted in outpatient infusions when compared to inpatient care. Most patients with acute porphyric attacks experience higher than average costs, because of hemodynamic instability, electrolyte abnormalities, severity of attacks, and duration of hospital stays. The current cost to the pharmacy for a vial of Panhematin of 350 mg, which is reconstituted, is ~$7230. Currently in the USA, in-patient stays are reimbursed by DRG [Diagnosis Related Groups] codes attached to principal diagnoses. Medicare and Medicaid reimbursements are based on DRGs for in-patient admissions. AIP falls under the DRG 642, which denotes Inborn and other Disorders of Metabolism. For this DRG, the standard reimbursement for in-patient admissions is only $5409, regardless of the length of stay and pharmacy costs. As already described, based on these specific patients' insurance providers [NC Medicaid and US Medicare], a standard reimbursement of only $5700 is provided to our health care system for each admission for exacerbation of AIP. High costs for drugs, primarily due to heme costs, are not considered as a separate entity for reimbursement in an inpatient admission. So, in an in-patient setting, most of the actual total

costs for typical 4–6 day admissions for patients with acute porphyric attacks are not adequately reimbursed. This lack of adequate reimbursement has led some hospitals and medical centers to be reluctant to, or even to refuse outright, recurrent hospital admissions for the unfortunate patients with acute hepatic porphyrias and frequent recurrent acute attacks [D. Howe, personal communication].

In comparison, even though specific national cost data are not available, out-patient management is typically less costly than in-patient. Specifically, as regards patients with acute hepatic porphyrias, our Center, as well as ~ 1/3 of all hospitals in the USA, which serve indigent, as well as well-insured patients, receive substantial discounts on drugs administered in the out-patient setting. This is possible because of the federal drug discount program established in Section 340B, 42 USC, of the Public Health Service Act, which mandates that drug manufacturers that participate in the Medicaid drug rebate program provide discounts on drugs administered to outpatients.

Because of the well-known potential complications of IV heme therapy, which include phlebitis, fever, iron overload and rare severe thrombotic events, its use should be limited to patients with well-established and confirmed diagnoses of acute hepatic porphyrias [6,17]. Nevertheless, for the relatively unusual patients like the two described herein, prophylactic IV heme can have a markedly favorable impact, both upon total health-care costs and upon quality-of-life. Although lesser frequencies of infusions [e.g., once every two or three weeks, or only during the week prior to usual monthly onset of symptoms of AIP in women with monthly attacks related to their menstrual cycles] have sometimes been tried by us and others, in general, we have not found such alternative regimens to be as reliably effective as one infusion per week.

Also worthy of note is that the over-excretions of ALA and PBG generally continue to be manifest during the weekly prophylactic infusions of heme, yet the frequency of acute attacks is much diminished. For example, our patient 2 had excretions at baseline [just prior to weekly IV heme infusions] of 72, 64, 67, 59 and 38 mg ALA/g creatinine and,102, 103, 95, 104, and 56 mg PBG/g creatinine during one 5 week stretch. Yet, he did not experience any acute attacks. These observations point up an enduring mystery about the acute hepatic porphyrias, namely, that there is not a very clear relationship between the overproduction of ALA and PBG and the development of acute attacks. Nevertheless, it does remain true that, whatever the chronic 'baseline' production of ALA and PBG are, they are significantly higher when patients develop acute attacks [16]. Contrary to recent suggestions of Schmitt et al., who suggested that prophylactic heme use was associated with increased acute attacks [15], we have not found that the administration of IV heme for valid cause and reasons [treatment of acute attacks and prevention of recurrent attacks of acute hepatic porphyrias], leads to any increased incidence of recurrent attacks. Their suggestion seems rather unlikely a priori because only patients with pre-existent recurrent and frequent symptoms will be those who will be treated with repeated heme infusions. We also note that close examination of the key figure of Schmitt et al. reveals that the apparent frequency of recurrent attacks in France already was increasing *before* the institution of prophylactic heme arginate therapy.

6. Conclusion

In conclusion, our subjects experienced better quality of life with weekly planned prophylactic IV heme, when compared to ED and inpatient management of acute attacks in cases with recurrent acute attacks of AIP. Weekly regimens also significantly reduced both direct and total costs for the health care systems and led to better reimbursements to our healthcare system. We suggest that, in carefully selected and appropriate patients, a planned weekly out-patient regimen with a multi-disciplinary approach, will prove beneficial for the well-being of similar patients with acute hepatic porphyrias, and also facilitate more efficient, humane, and appropriate health care delivery. Additional multi-center prospective studies in carefully selected patients would likely help us to understand better the qualitative and cost benefits of prophylactic heme infusions in patients with severe symptomatic AIP.

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