

Original Investigation

Lactulose vs Polyethylene Glycol 3350-Electrolyte Solution for Treatment of Overt Hepatic Encephalopathy

The HELP Randomized Clinical Trial

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IMPORTANCE Hepatic encephalopathy (HE) is a common cause of hospitalization in patients with cirrhosis. Pharmacologic treatment for acute (overt) HE has remained the same for decades.

OBJECTIVE To compare polyethylene glycol 3350–electrolyte solution (PEG) and lactulose treatments in patients with cirrhosis admitted to the hospital for HE. We hypothesized that rapid catharsis of the gut using PEG may resolve HE more effectively than lactulose.

DESIGN, SETTING, AND PARTICIPANTS The HELP (Hepatic Encephalopathy: Lactulose vs Polyethylene Glycol 3350-Electrolyte Solution) study is a randomized clinical trial in an academic tertiary hospital of 50 patients with cirrhosis (of 186 screened) admitted for HE.

INTERVENTIONS Participants were block randomized to receive treatment with PEG, 4-L dose (n = 25), or standard-of-care lactulose (n = 25) during hospitalization.

MAIN OUTCOMES AND MEASURES The primary end point was an improvement of 1 or more in HE grade at 24 hours, determined using the hepatic encephalopathy scoring algorithm (HESA), ranging from 0 (normal clinical and neuropsychological assessments) to 4 (coma). Secondary outcomes included time to HE resolution and overall length of stay.

RESULTS A total of 25 patients were randomized to each treatment arm. Baseline clinical features at admission were similar in the groups. Thirteen of 25 patients in the standard therapy arm (52%) had an improvement of 1 or more in HESA score, thus meeting the primary outcome measure, compared with 21 of 23 evaluated patients receiving PEG (91%) ($P < .01$); 1 patient was discharged before final analysis and 1 refused participation. The mean (SD) HESA score at 24 hours for patients receiving standard therapy changed from 2.3 (0.9) to 1.6 (0.9) compared with a change from 2.3 (0.9) to 0.9 (1.0) for the PEG-treated groups ($P = .002$). The median time for HE resolution was 2 days for standard therapy and 1 day for PEG ($P = .01$). Adverse events were uncommon, and none was definitely study related.

CONCLUSIONS AND RELEVANCE PEG led to more rapid HE resolution than standard therapy, suggesting that PEG may be superior to standard lactulose therapy in patients with cirrhosis hospitalized for acute HE.

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← Invited Commentary
page 1734

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Hepatic encephalopathy (HE) includes a spectrum of reversible neuropsychiatric abnormalities occurring in patients with cirrhosis who exhibit signs and symptoms of mild to severe cognitive dysfunction such as a reversal of sleep patterns, abrupt change in behavior, altered mentation, or coma.¹ The mechanisms causing brain dysfunction in HE are still not well understood, although it is commonly believed that ammonia produced by gut bacteria is an important contributing factor.²

Lactulose (beta-1,4-galactosido-fructose) has been the standard-of-care treatment for acute management of HE for decades.³ The mechanism of action of lactulose is controversial and is postulated to be the trapping of ammonium ions in the gut by organic acids released after bacteria metabolize lactulose or the removal of ammoniogenic organisms and/or replacement of these species with acidophilic bacteria lacking urease.^{4,5} Others have suggested that inhibition of intestinal glutamine uptake and subsequent decreased ammonia-generation plays a role.⁶

Laxative agents such as magnesium salts were used prior to the introduction of lactulose,⁷⁻⁹ suggesting that catharsis alone may be effective for treatment of HE. However, since the first report of the efficacy of lactulose in 1966,⁵ and the consequent widespread adoption of nonabsorbable disaccharides for treatment of HE, there have been few studies com-

paring their effect with cathartic methods.⁴ Since polyethylene glycol 3350–electrolyte solution (PEG) is a safe, commonly used, and highly effective purgative, we hypothesized that if immediate catharsis of the gut is important in the treatment of acute (overt) HE, then PEG may be superior to lactulose in this capacity. The objective of this study was to determine whether PEG may represent an additional therapeutic option for treatment of patients with overt HE.

Methods

The HELP (Hepatic Encephalopathy: Lactulose vs Polyethylene Glycol 3350–Electrolyte Solution) study was approved by the University of Texas Southwestern Medical Center institutional review board and by the Parkland Health and Hospital System. All patients provided written informed consent through their legally authorized representatives (LARs) prior to their participation.

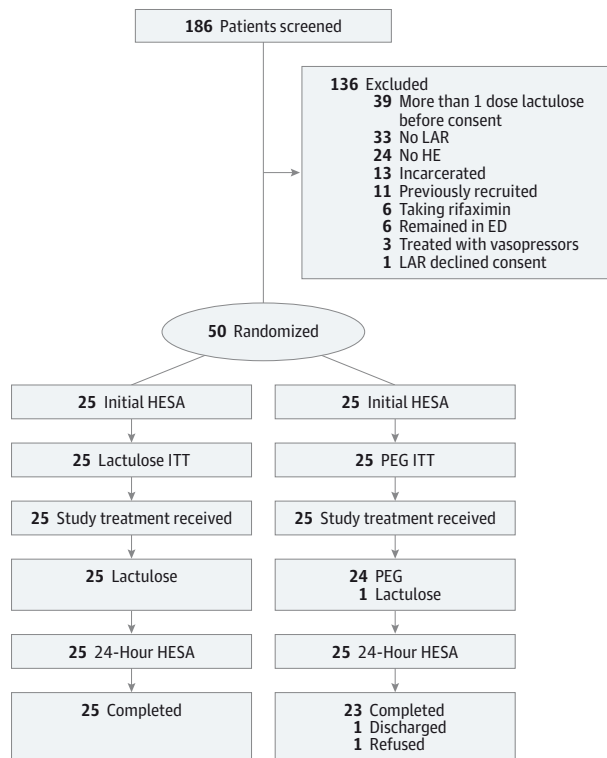
Patient Selection

This randomized clinical trial was performed at Parkland Memorial Hospital, Dallas, Texas, from January 2011 to June 2012. All patients presenting to the emergency department with known cirrhosis and altered mental status (AMS) were eligible. For study purposes, HE was defined as AMS with typical symptoms and signs in the absence of an obvious cause of AMS, as previously described.^{1,10,11} The causes of cirrhosis were ascertained and precipitating factors identified by 2 team members. Participant inclusion criteria were as follows: age 18 to 80 years; diagnosis of cirrhosis from any cause; presence of any grade of HE; and the availability of an LAR for interview and consent. Exclusion criteria were as follows: acute liver failure, defined as coagulopathy (international normalized ratio >1.5) with any degree of AMS in the absence of underlying chronic liver disease (CLD)¹⁰; AMS from a cause other than HE¹¹; treatment with rifaximin or neomycin within the previous 7 days; receipt of more than 1 dose of lactulose prior to consent; lack of an LAR to provide consent; refusal of consent by the LAR; previous participation in the present study; hemodynamic instability treated with vasopressors; pregnancy; or being a prisoner (Figure 1).

Definitions

Cirrhosis was defined by clinical features, including a history consistent with CLD as well as a documented complication of CLD (ie, ascites, varices, hepatic encephalopathy)¹² and/or imaging results consistent with cirrhosis and/or liver histologic findings consistent with cirrhosis.¹³ The process by which the specific type of cirrhosis was ascertained is described in the eAppendix and eTables in the Supplement. Potential causes of HE at the time of admission were also evaluated and are defined in the eAppendix in the Supplement. Grade of HE was determined by using the hepatic encephalopathy scoring algorithm (HESA), which has been shown to be an objective scoring instrument (and better than the West Haven criteria).¹⁴ Resolution of HE was defined as an improvement in HESA to grade 0, patient discharge, patient death, or 2 consecutive days

Figure 1. Flow Diagram of Patient Recruitment, Randomization, and Follow-up



ED indicates emergency department; HE, hepatic encephalopathy; HESA, HE scoring algorithm; ITT, intention to treat; LAR, legally authorized representative; and PEG, polyethylene glycol 3350–electrolyte solution.

when HESA grade remained at 1 after an initial improvement in at least 1 full grade.

Patient Recruitment and Participant Randomization

When the diagnosis of HE was suspected, the study team was notified. The protocol stipulated that potential participants could be treated with a single dose of lactulose prior to randomization. Furthermore, by design, the amount and route of administration were at the discretion of the first health care professional to administer care. After assessment of eligibility, a member of the study team interviewed the patient's LAR. If the LAR agreed to participate and consent was provided, an opaque sealed envelope was opened. The envelope included a computer-generated number and treatment assignment. The a priori block randomization included 8 blocks of 6 patients each distributed in a 1:1 fashion according to the statistical analysis described herein. The random code sequence was blinded from the study investigators.

After patient enrollment and HESA evaluation on admission, patients received either PEG or standard-of-care therapy, prescribed by the treating physician. The standard control treatment consisted of lactulose, 20 to 30 g administered orally or by nasogastric tube (3 or more doses within 24 hours) or 200 g by rectal tube if oral intake was not possible or inadequate, at the discretion of the treating physician. The study treatment consisted of 4 L of PEG administered orally or via nasogastric tube, again at the discretion of the treating physician. PEG was administered in a single dose over 4 hours. After PEG administration, no lactulose (or other potential HE therapy) was allowed for 24 hours, at which time the follow-up HESA score was obtained. After 24 hours, patients were allowed to receive lactulose per the standard of care. Patients using rifaximin were excluded; its use was limited to lactulose failures at our institution and was not part of the study protocol. Clinical variables including adverse events and HESA scores were collected daily until the patient refused, was discharged home, or died during the hospitalization.

HESA Testing

Permission to administer the HESA was obtained from the Technology Transfer Office of the University of California, San Diego. Two study team members (R.S.R. and D.C.R.) were certified for clinical and neuropsychiatric testing. Both the initial and the 24-hour follow-up HESAs were completed by 1 study team member (R.S.R.) for all patients. Different HESA versions were used during follow-up testing at 24 hours to prevent learning and recall bias. The 24-hour interval was chosen to minimize differences in circadian rhythm.

Safety Measures

Prior to study initiation, a US Food and Drug Administration exemption status was granted for the investigational use of PEG. Interim safety analyses were carried out by an independent data safety monitoring board (DSMB) after 12, 24, and 36 patients were enrolled. All adverse events were reported to the University of Texas Southwestern Medical Center institutional review board and reviewed by the DSMB.

Statistical Methods

The primary outcome measure was improvement of 1 or more in HESA score at 24 hours. Previous literature indicates that the overall improvement for patients with HE treated with lactulose or lactitol compared with placebo or no intervention is 46% to 100%.³ Thus, we estimated that a conservative lactulose response rate would be 0.55. With a predicted response rate for PEG of 0.90, a 2-sided α of .05, and power of 0.8, we estimated that to identify the predicted effect size, a total sample size of 48 (24 in each group) would be required to demonstrate a statistically significant difference in outcomes. We aimed to recruit 54 patients (9 blocks with 6 patients in each block) to account for possible dropouts; enrollment was halted at 50 patients since the dropout rate was lower than expected (4%; $n = 2$).

Demographics and laboratory test results were collected for all patients and entered into a Microsoft Access database and a FileMaker database. Data were entered separately (in duplicate) by 2 team members, who independently determined the causes of the cirrhosis and identified the precipitating factors; discrepancies were resolved via consensus. Child-Turcotte-Pugh scores^{15,16} and scores for Model of End-stage Liver Disease with United Network for Organ Sharing modification¹⁷ were calculated using admission data and standard criteria. Continuous variables were compared using the *t* test, Kaplan-Meier analysis, or Wilcoxon rank-sum (Mann-Whitney) tests; categorical variables were compared with χ^2 or Fisher exact tests. All analyses were intention to treat. Statistical analysis was performed using Stata software, version 12.1 (StataCorp LP).

Results

Study Cohort

A total of 186 patients were screened; 50 eligible patients were randomized to standard-of-care treatment (lactulose) or PEG. The most common reasons for exclusion were that the patient had received more than 1 dose of lactulose in the emergency department prior to consent, that a LAR was not available, or that the patient did not have HE (Figure 1). The cohort was typical of patients with cirrhosis, with a male predominance and mean age of 56 years (Table 1).

Comparison of Treatment Groups

The 2 groups were similar with respect to demographics and clinical features (Table 1). The precipitants of HE included a total of 80 potential contributing factors identified in 50 patients (eTable 1 in the Supplement). Admission laboratory data were also similar in the 2 groups (Table 1), with the exception of blood urea nitrogen level, which was higher in the PEG group ($P = .03$). Admission ammonia levels were elevated in both groups (Table 2). Nineteen patients in the lactulose group and 18 patients in the PEG group underwent head computed tomography (CT) scanning. No acute CT findings were identified in any patient.

Results of Treatment

Following consent for study entry, patients were randomly assigned to receive either standard-of-care (lactulose) or PEG

Table 1. Demographics and Clinical Data

Characteristic	All Patients (N = 50)	Lactulose Group (n = 25)	PEG Group (n = 25)
Age, mean (SD), y	56 (9)	56 (11)	56 (7)
Women, No.	19	10	9
Race/ethnicity, No.			
African American	4	2	2
Asian	1	0	1
White, Hispanic	35	15	20
White, non-Hispanic	10	8	2
Cirrhosis cause			
Alcoholic liver disease ^a	19 (38)	9 (36)	10 (40)
Cryptogenic ^b	12 (24)	6 (24)	6 (24)
Hepatitis C ^c	17 (34)	9 (36)	8 (32)
Hepatitis B ^d	2 (4)	1 (4)	1 (4)
WBC count, mean (SD), ×10 ⁹ /L	6.2 (2.6)	6.2 (2.6)	6.3 (2.6)
BUN, mean (SD), mg/dL	26 (15)	21 (11)	30 (17)
Creatinine, mean (SD), mg/dL	1.41 (1.02)	1.12 (0.52)	1.70 (1.29)
Total bilirubin, mean (SD), mg/dL	3.3 (2.3)	2.9 (1.4)	3.6 (3.0)
INR, mean (SD)	1.5 (0.4)	1.4 (0.3)	1.5 (0.4)
Albumin, mean (SD), g/dL	2.7 (0.6)	2.8 (0.5)	2.7 (0.6)
MELD score, mean (SD)	17 (5)	17 (5)	17 (6)
CTP score, mean (SD)	10 (2)	10 (1)	10 (2)

Abbreviations: BUN, blood urea nitrogen; CTP, Child-Turcotte-Pugh; INR, international normalized ratio; MELD, Model of End-stage Liver Disease; PEG, polyethylene glycol 3350–electrolyte solution; WBC, white blood cell.

SI conversion factors: To convert BUN to millimoles per liter, multiply by 0.357; creatinine to micromoles per liter, multiply by 88.4; bilirubin to micromoles per liter, multiply by 17.104; and albumin to grams per liter, multiply by 10.

^a Alcoholic liver disease was defined as alcohol consumption of more than 60 g/d for more than 10 years and no viremia for hepatitis B or hepatitis C.

^b Cryptogenic causes (n = 12) were defined as nonalcoholic fatty liver disease with nonalcoholic steatohepatitis found on biopsy (n = 1 of 12) or no alternative diagnosis and with presence of risk factors (eg, diabetes mellitus, obesity, Hispanic ethnicity) (n = 11 of 12).

^c Hepatitis C was defined as viremia (n = 16 of 17) or positive serologic findings and no alternative cause (n = 1 of 17).

^d Hepatitis B was defined as viremia.

Table 2. Study Outcomes

Characteristic	Total (N = 50)	Lactulose (n = 25)	PEG (n = 25)	P Value ^a
24-h HESA score change, mean (SD)	1.1 (0.8)	0.7 (0.8)	1.5 (0.8) ^b	.002
Length of stay, d	6 (9)	8 (12)	4 (3)	.07
6- to 24-h Ammonia, mean (SD), μmol/L ^c	(n = 33)	(n = 15)	(n = 18)	
Baseline	159 (73)	175 (70)	146 (75)	.19
After study	103 (51)	82 (29)	120 (60)	.049
Difference	56 (88)	93 (71)	26 (90)	.03

Abbreviations: HESA, hepatic encephalopathy scoring algorithm; PEG, polyethylene glycol 3350–electrolyte solution.

^a Control (lactulose) and experimental (PEG) groups were compared using Wilcoxon (Mann-Whitney) rank-sum tests for ammonia and HESA score, Kaplan-Meier analysis for length of stay, and Fisher exact test for categorical variables.

^b Twenty-four hour HESA score was missing from 2 patients in the PEG group: one was competent and refused testing, the other was discharged in less than 24 h; thus, the 24-h HESA score change was calculated for 23 patients.

^c Ammonia levels at 6 to 24 hours were not available for all patients.

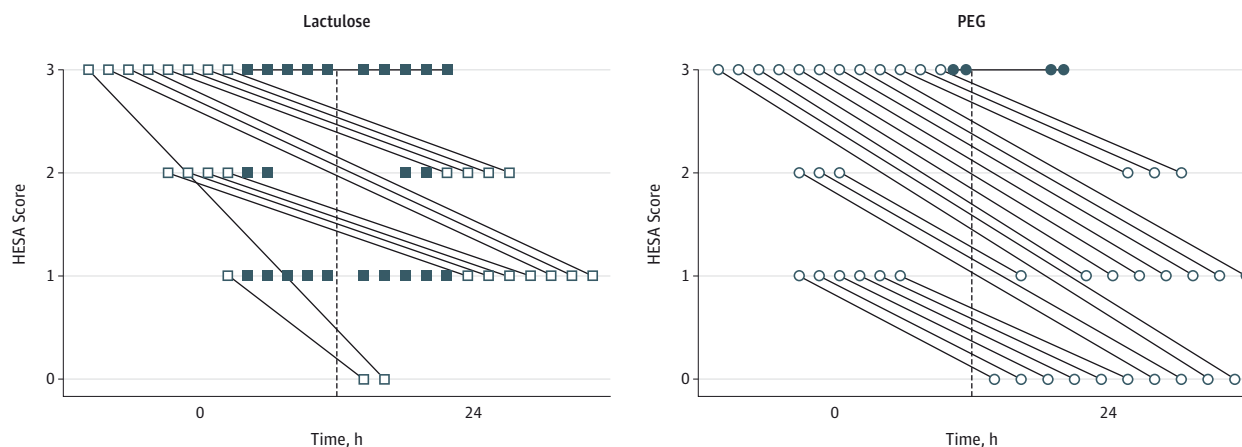
therapy. Of note, 1 patient in the PEG group did not receive the allocated treatment (unable to ingest PEG orally, and a nasogastric tube could not be placed) and so was treated with a lactulose enema. There were no significant differences between the groups with regard to the initial dosing with lactulose ($P = .45$) (eTable 2 in the Supplement).

We measured the results of treatment by comparing initial and 24-hour HESA scores (Figure 2). Two patients in the PEG group did not have follow-up HESA scores. One patient

became alert and oriented and refused assessment; the second patient improved to point of discharge home in less than 24 hours. Consequently, these 2 patients were not included in either the initial or 24-hour analysis. Initial HESA scores were identical (mean 2.3; $P = .70$), and there were no differences in the distribution of the scores ($P = .62$).

Nine of 25 total patients in the lactulose group (36%) had an incremental improvement of 1 HESA grade; 3 (12%) improved by 2 grades; and 1 (4%) improved by 3 HESA grades at

Figure 2. Change in HESA Grade With Treatment



The initial (hour 0) and follow-up (hour 24) HESA scores are depicted for the lactulose control (A) and PEG experimental (B) groups. Each transparent symbol represents a patient whose HESA score had changed from 0 to 24

hours; solid symbols represent patients whose HESA score showed no change at 24 hours. HESA indicates hepatic encephalopathy scoring algorithm; PEG, polyethylene glycol 3350-electrolyte solution.

24 hours; 12 of 25 patients had no improvement (48%) (Figure 2). Only 2 (8%) had a HESA score of 0 at 24 hours.

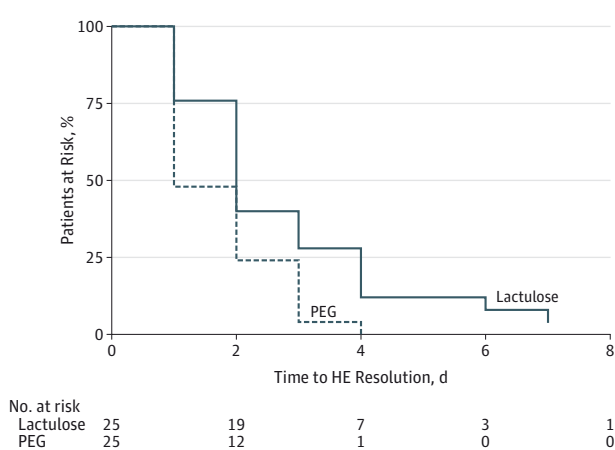
In contrast, in the PEG group, 10 of 23 patients improved by 1 HESA grade at 24 hours (43%); 9 (39%) by 2 grades; and 1 (4%) by 3 grades; 2 (9%) of 23 patients receiving PEG had no improvement (Figure 2). Ten patients in the PEG group (43%) had a HESA score of zero at 24 hours.

Patients receiving PEG had a significantly lower mean (SD) HESA score at 24 hours than patients receiving lactulose (0.9 [1.0] vs 1.6 [0.9]; $P = .002$). By intention-to-treat analysis, the distribution of HESA categories was also significantly different in the 2 groups ($P = .04$). The majority of patients in the PEG arm (76%; $n = 19$) received the full 4-L dose of PEG within the time allotted. The proportion of patients having a nasogastric tube placed for drug administration did not differ (12% [$n = 3$] and 16% [$n = 4$] for lactulose and PEG, respectively). A total of 5 patients in the lactulose arm received rectal lactulose; 1 of these patients (20%) had improvement in HESA grade at 24 hours. The median time to HE resolution was 1 day in patients receiving PEG compared with 2 days in those receiving standard-of-care lactulose ($P = .01$) (Figure 3).

Adverse Events

Both PEG and standard-therapy lactulose were considered safe therapies with no definitive related adverse events. Of the reported 8 serious adverse events (5 control group, 3 PEG group), none were considered to be definitely or probably related to the study medications. Four events in the lactulose group were definitely not related, while 1 was possibly related. In the PEG group, 1 of the 3 events was definitely not related, and 2 were possibly related. Two patients in the lactulose arm died; both died from cardiorespiratory arrest after being transitioned to comfort care only. One patient in the PEG arm died after completion of the PEG treatment from complications of hemoperitoneum. In the 3 cases in which adverse events were classified as possibly study related, 2 patients developed re-

Figure 3. Time to Hepatic Encephalopathy (HE) Resolution



Shown is a Kaplan-Meier graph depicting the proportion of patients at risk for HE who received either standard-of-care lactulose therapy or polyethylene glycol 3350-electrolyte solution (PEG). Patients receiving PEG had more rapid resolution of HE than those receiving lactulose ($P = .01$).

current HE more than 24 hours after completion of PEG treatment, and 1 patient in the lactulose group refused oral lactulose treatment more than 24 hours after study treatment was given.

Overall, treatment regimens were similar in terms of tolerability, with the exception that in the lactulose arm, there was more bloating, while PEG patients experienced more diarrhea symptoms. Furthermore, over 50% of patients who received PEG not only preferred the “salty” taste over the sweet flavor of lactulose, they requested this therapy at discharge to replace their current outpatient lactulose regimen.

The possibility that treatment may alter electrolyte levels or renal function in the follow-up period was also assessed (eTable 3 in the Supplement). Electrolytes, creatinine, and

blood urea nitrogen were measured at baseline and at 6 to 24 hours after admission. Potassium levels decreased from 4.3 mmol/L to 3.8 mmol/L (the conversion to milliequivalents per liter is a 1-to-1 conversion) after PEG administration ($P = .006$). Six patients in each of the PEG and lactulose groups had moderate hypokalemia (potassium levels <3.5 mmol/L) during the first 6 to 24 hours after treatment. There were no significant changes in levels of serum sodium, creatinine, or blood urea nitrogen after either PEG or lactulose treatment.

Discussion

The results of this study indicate that bowel cleansing with PEG, normally used for colonoscopy preparations, is a safe, rapid, and effective immediate treatment strategy for patients presenting with acute overt HE. When compared with lactulose, the current standard treatment for overt HE, objective measures of HE improved significantly faster in those receiving PEG. By accelerating improvement in mentation, initial treatment with PEG has the potential to not only shorten hospitalizations but also permit health care professionals to concentrate on managing the precipitating factors and identifying other causes of metabolic encephalopathy that may be present.

Although long studied, the exact mechanisms resulting in overt HE in patients with cirrhosis are not completely defined.¹⁸⁻²⁰ Disruption of the normal metabolism of ammonia is almost uniformly proposed as having pathophysiologic relevance. Numerous studies have indicated a central role for gastrointestinal bacteria,^{3,21} and their importance is strongly suggested by the parallel responses observed with antibiotics and bowel cleansing. Unlike the nonabsorbable disaccharides, antibiotic regimens have evolved over decades, from systemic agents through less absorbable compounds with decreasing adverse effects. Rifaximin, a newer antibiotic without the ototoxic profile of neomycin, targets gastrointestinal bacteria, with efficacy against coliforms such as *Escherichia coli* that can express urease and thereby produce ammonia.²²

It has been postulated that at least 1 mechanism for the development of acute HE is the generation of excess ammonia by gastrointestinal bacteria, and that ammonia cannot be metabolized when the liver is diseased or bypassed. PEG is not absorbed and, unlike lactulose, lacks the unabsorbed carbohydrate load that lowers stool pH and increases stool water losses.^{23,24} Furthermore, ammonia excretion in the stool is greater with PEG than with lactulose.²³ However, an interesting observation in our study was that the 24-hour difference in ammonia was greater in the lactulose group (ie, overall lower ammonia level) than in the PEG group (Table 2).

However, ammonia levels did not correlate with better improvement in HESA grades. Possible explanations for this result include the mechanism of action of the 2 study medications²³ and the timing of the posttreatment ammonia levels. Since PEG is a highly effective cathartic, the potential clinical improvement in HE might precede and be more clinically relevant than the actual decrease in ammonia levels,

which would parallel our hypothesis. Alternatively, circulating ammonia levels may return to their elevated baseline faster (and before clinical deterioration is manifested). PEG treatment may also result in dehydration and decreased renal perfusion, which might lead to decreased renal ammonia excretion. (Of note, all patients required long-term therapy.)

Finally, we examined ammonia levels from 6 to 24 hours after medication ingestion, a time at which ammonia levels might be expected to be rapidly changing as a result of therapy. We believe that future studies evaluating ammonia and its correlation with HE resolution will help clarify this issue.

An important consideration with the use of PEG is that it causes a substantial catharsis and thus in theory may result in dehydration, electrolyte disturbances, and even acid-base abnormalities. However, it also contains electrolyte additives that help balance water and electrolyte loss across the gastrointestinal tract and is the most commonly used cathartic for patients requiring a colon preparation. Indeed, it has been shown to be safe and effective in a wide variety of patients.²⁵ In our experience, lactulose, which functions as an osmotic diarrheal agent, causes much more severe electrolyte disturbances than does PEG.

The major strengths of the present study are its innovative approach and potential generalizability. PEG preparations are widely available, commonly used, and inexpensive. One potential benefit of using PEG for overt HE is that it may result in shorter lengths of stay, depending on the causes of the HE; HE resolution was shown to be significantly more rapid in the PEG group, and the length of hospital stay was shorter. This could potentially result in a decrease in the total direct costs of hospitalization nationally. For example, data from the Healthcare Cost and Utilization Project (HCUP), a national repository of patient-level hospital care data, reveal that from 2003 to 2011, substantial increases have occurred for the number of discharges (40 012 to 50 048) and the cost for HE (\$23 192 to \$38 130).²⁶ Although HCUP data over the past 9 years likely underestimate the incidence of HE, since it is not always a primary diagnosis, our data point to the potential for substantial cost savings.

We recognize potential limitations of this study. First, it is from a single center and thus may not be generalizable to other centers. However, we would emphasize that it was performed in a center with a highly diverse population. Second, this study could not be blinded, since giving a placebo in the place of PEG was not possible. In addition, we recognize that the treatments could be determined if desired by taking a specific history (eg, ingestion of a sweet or salty liquid for lactulose or PEG, respectively). To mitigate the inability to blind, we included an element of blinding by arranging for a separate investigator (A.G.S.) to obtain consent, randomize, and ensure that appropriate study medication was provided to a limited number of patients. In this manner, a different investigator could administer the HESA in a blinded fashion when feasible. Furthermore, the results of each HESA instrument, which relies heavily on neuropsychiatric testing, was documented and later graded 24 hours after its administration with independent review of the results completed at separate time intervals by 2 investigators.

Conclusions

We describe herein a novel approach to the early management of an acute presentation of overt HE. Compared with lactulose treatment, the current standard of care for acute HE in hospitalized patients, a single dose of PEG significantly improved the overall grade of encephalopathy in the first 24 hours, reduced days to HE resolution, and appeared to lead to shorter length

of stay. Since PEG treatment is commonly and widely used (ie, for bowel preparation), simple to administer, and apparently safe in this population, we believe that the results of this study should be generalizable to most patients with acute HE. Certainly, the effects of PEG are transient, and follow-up therapy to prevent recurrence of HE in those with chronic symptoms is important. Also, further studies are needed to better understand whether the use of PEG could improve the quality of care and/or reduce important quality metrics such as length of hospital stay.

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Author Contributions: Drs Rahimi and Rockey had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rahimi, Rockey.

Acquisition, analysis, or interpretation of data: All authors.

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