Considerations for the Cost-Effective Management of Hepatic Encephalopathy

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Hepatic encephalopathy (HE) is a neuropsychiatric condition that is usually associated with acute or chronic liver disease. The overall prevalence of HE among patients admitted to the hospital is approximately 0.3% in the United States, but the incidence and prevalence are much higher in some patient populations, such as those with cirrhosis.[1] Cirrhosis is the most common cause of HE. In an analysis of National Health And Nutrition Examination Survey data from 1999 and 2010, the estimated prevalence of cirrhosis was 0.27% in American adults, corresponding to more than 630,000 adults.[2] However, this may be a large underestimate of the affected population as 69% of cirrhotic cases are undiagnosed.[2] As many as 80% of patients with cirrhosis will experience some form of HE during their lifetime, with an estimated nationwide incidence of 115,814 affected patients in 2009.[1,3,4] HE poses a substantial economic burden; factors contributing to the total cost of HE include medication cost, morbidity and mortality, quality of life, cost of treatment, marketing, and research and development. Over the last 2 decades, hospitalization costs associated with HE have been rapidly increasing. From 1994 to 2003, hospitalization costs associated with HE totaled $5.9 billion, while hospitalization costs in 2003 alone totaled $1.3 billion.[5] HE-related hospitalization costs have continued to rise; these costs escalated from $4.68 billion in 2005 to $7.25 billion in 2009.[1]

Classification

HE is classified into types A, B, and C based on the etiology. Type A HE is secondary to acute liver failure; Type B is associated with portosystemic bypass without liver disease; and type C is secondary to chronic liver disease.[3] Clinical severity of HE is graded by the West Haven Criteria (Grades I through IV) (**Table 1**[3]) and neurocognitive impairment is graded by the Spectrum of Neuro-Cognitive Impairment in Cirrhosis (SONIC).[3] HE can be broadly categorized as covert hepatic encephalopathy (CHE), which includes subclinical or minimal HE (MHE) and grade I HE, or the more severe overt hepatic encephalopathy (OHE), which encompasses grades II through IV HE. Patients with HE may experience episodic bouts, developing over a short time period and exerting sporadic effects, or persistent HE, impairing daily function.[6]

ABSTRACT

Hepatic encephalopathy (HE) is a neuropsychiatric complication commonly associated with liver disease, namely cirrhosis. The inability of the liver to metabolize ammonia results in a buildup of ammonia, which can cross the blood–brain barrier and cause significant neurocognitive impairment. Up to 80% of patients with cirrhosis will experience HE and a large proportion of these patients are at high risk of recurrent HE. There are several factors to consider when developing a cost-effective approach to managing HE, such as patient compliance, the adverse event (AE) profile of drug therapy, efficacy of drug therapy, and relative cost–benefits of drug therapy. Pharmacologic agents used for HE treatment and prevention are commonly associated with gastrointestinal AEs, namely diarrhea. While these AEs are mild in nature, they can be bothersome and lead to patient noncompliance, which increases the patient's risk of HE. Furthermore, the complex dosing schedule and self-titration requirement of lactulose, a first-line agent, can be confusing to a patient. A patient's noncompliance with self-titration may result in underuse, increasing the patient's risk of HE, or overuse, increasing the patient's risk of severe AEs. HE imposes a significant economic burden to the patient, patients' caregivers, healthcare systems, and society. HE not only negatively impacts a patient's morbidity and mortality, but also impacts the patient's psychological and social functioning and overall quality of life. HE can impact the patient's ability to work, resulting in reduced productivity and lost wages. A patient with HE may require hospitalization, which accounts for a substantial proportion of costs associated with HE. Given the social and financial burden of HE, cost-effective management of HE is crucial. Early prevention is important to minimize the societal and economic costs associated with HE.

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TABLE 1. Grading of Hepatic Encephalopathy (HE) Utilizing West Haven Criteria[3]

Grading	Signs & Symptoms	Time Course
Covert		
Minimal HE	Abnormal results on psychomotor/neuropsychological tests without clinical evidence of mental status changes	Episodic
1	Minor neuropsychological changes such as anxiety, impaired basic math abilities, and altered sleep patterns	Episodic/recurrent
Overt		
2	Noticeable changes of lethargy, time disorientation, personality changes, or impaired coordination	Recurrent
3	Confusion, somnolence/stupor, inappropriate strange behavior	Recurrent/persistent
4	Coma, no response to painful stimuli	Recurrent/persistent

Risk Factors

Several risk factors and predictive factors are associated with the development of HE. Among patients with cirrhosis, between 20% and 80% will experience CHE and 30% will experience OHE during their course of disease.[3,4] Moreover, OHE is present in approximately 14% of all patients at the time of cirrhosis diagnosis; between 16% and 21% of patients diagnosed with decompensated cirrhosis and between 10% and 50% of patients with a transjugular intrahepatic portosystemic shunt (TIPS) will have OHE at the time of diagnosis.[3] Other risk factors associated with OHE include diabetes and hepatitis C infection, as well as complications of cirrhosis including CHE, infection, variceal bleeding, and ascites.[3]

Clinical Presentation

The clinical presentation of HE varies widely by disease severity and neurocognitive impairment. In MHE, patients might not have obvious clinical changes but instead may have abnormal psychometric tests indicating mild neurocognitive decline. Grade I HE is marked by subtle behavioral changes, such as sleep disturbances, inattention, and moodiness. Upon progressing to OHE, patients may exhibit drastic personality changes, irritability, motor impairment, speech slowness, and excessive daytime sleepiness.[3,7,8]

OHE has a high risk of recurrence within a short time period, even if the patient has mild symptoms or is receiving treatment. Within 1 year of an OHE episode, patients have a 40% cumulative risk of another recurrence. Despite treatment with lactulose, patients who have had recurrent episodes of OHE have a 40% risk of recurrence within 6 months. For patients with mild cognitive dysfunction, approximately 1 episode of OHE will occur for every

3 years of survival.[3] With this degree of recurrence, cost-effective management becomes imperative.

Pathogenesis

Under normal physiologic conditions, nitrogen compounds are typically derived from the gut and transported via portal circulation to the liver, where they then enter the urea cycle. The end product of ammonia metabolism is urea, which is excreted through urine. In advanced liver disease, damaged hepatocytes and portosystemic shunts are unable to properly metabolize and excrete nitrogen compounds, leading to a buildup of ammonia in extrahepatic tissues. Ammonia crosses the blood–brain barrier following the increased systemic concentration and is metabolized by glutamine synthetase in astrocytes, which causes morphologic abnormalities, such as astrocyte swelling.[7]

Furthermore, to adequately treat HE, the following provocative factors must be identified and corrected: increased nitrogen load (eg, gastrointestinal bleeding, renal failure), metabolic disorders (eg, hyponatremia, hypokalemia, dehydration), medications (eg, benzodiazepines, diuretics), bacterial infections, and TIPS.[9] Beyond ammonia dysregulation, other pathologic mechanisms of HE include blood–brain barrier disruption and neurotransmission abnormalities in GABAergic and benzodiazepine pathways.[9]

The Impact of HE on Clinical Outcomes

Patients who develop HE are at risk for poor clinical outcomes and reduced survival. Among patients with decompensated cirrhosis, the median survival is 2 years for a patient with OHE compared with 12 years for patients without OHE.[10] In an analysis of 271 patients with hepatic decompensation, OHE was associated with a significantly increased risk of mortality in patients with TIPS and grade III or IV HE compared with patients with grade 0 HE (HR, 3.68; 95% CI, 1.85-7.30; P = .0002). Increased risk of mortality in patients with TIPS and grade II HE was intermediate compared with patients with grade 0 HE (HR, 1.56; 95% CI, 0.98-2.50; P = .06). Even after adjustment for Model for End-Stage Liver Disease (MELD) scores, OHE remained significantly associated with risk of death (HR, 2.55; 95% CI, 1.72-3.78; P < .01).[11]

HE also negatively impacts transplant survival. In a retrospective analysis of approximately 60,000 patients who underwent a liver transplant between 2003 and 2013, grade III or IV HE was associated with significantly lower survival at 1 year compared with patients without HE. The survival rate for patients with grade III or IV HE was 82.5% compared with 90.3% in patients without HE (P <.001) at 1-year post transplant. The survival rate 5 years post transplant was 69.1% in patients with grade III or IV HE compared with 74.4% in patients without HE (P <.001). After multivariate regression adjusting for sex, age at time of transplant, comorbidities, and MELD scores, the presence of HE was associated with worse posttransplant survival (HR, 1.27; P <.001).[12]

MHE and grade I HE are associated with poor clinical outcomes as well. In part, this may be due to the approximately 2-fold increased

risk of OHE among this population.[13] In a prospective analysis of 170 patients with cirrhosis, survival was compared between patients with and without CHE. Compared with patients without CHE, those with CHE were at increased risk for hospitalization (HR, 2.5; 95% CI, 1.4-4.5; P = .002) and the composite outcome of death or transplant (HR, 3.4; 95% CI, 1.2-9.7; P = .01).[13] At 4-year follow-up, 75.6% of patients who experienced CHE died or underwent a transplant compared with 22.5% of patients without CHE.[13]

Available Management Strategies for Outpatient Care

The 2014 American Association for the Study of Liver Diseases and European Association for the Study of the Liver (AASLD/EASL) practice guidelines on hepatic encephalopathy in chronic liver disease currently recommend that only OHE should be routinely treated. Nonetheless, primary prophylaxis for HE is recommended in certain circumstances, in which patients may be at increased risk for the development of OHE. Other factors that might lead to treatment in patients with CHE include those with impairments in daily living, such as deficiencies in driving or poor work performance.[3] Precipitating factors for OHE should also be identified and treated preemptively.[3]

Pharmacologic Treatments

Lactulose

Lactulose, a nonabsorbable disaccharide, is among the most common treatments for OHE. Since lactulose is synthesized by fructose and galactose, it is not digestible in mammals and passes unabsorbed to the large intestine.[14] Metabolism of lactulose by colonic bacteria to produce lactic, acetic, and formic acids acidifies the colonic contents, preventing the growth of ammonia-producing bacteria, promoting the growth of beneficial microorganisms, and decreasing ammonia load by changing ammonia to ammonium, which is not absorbed.[15] Lactulose syrup (25 mL) is typically given every 1 to 2 hours until at least 2 soft or loose bowel movements are produced per day, at which time dosing is titrated to maintain 2 to 3 bowel movements per day. Overusing lactulose can potentially lead to dehydration, hypernatremia, or aspiration, and may even precipitate HE.[3]

The efficacy of lactulose was assessed by a Cochrane review meta-analysis of 1415 patients enrolled in 22 randomized controlled trials (RCTs). The meta-analysis included both primary and secondary prophylaxis studies which were conducted internationally between the years 1969 and 2014. Results indicated that nonabsorbable disaccharides were associated with improvement or resolution of HE when compared with placebo or no intervention (risk ratio [RR], 0.58; 95% CI, 0.50-0.69).[16] Lactulose reduced adverse events (AEs) of underlying liver disease, which included liver failure, hepatorenal syndrome, and variceal bleeding (RR, 0.47; 95% CI, 0.36-0.60).[16] In a separate meta-analysis of 9 RCTs, lactulose significantly lowered the mean number of abnormal neuropsychological tests compared

with placebo or no intervention (weighted mean difference [WMD]: −1.76; 95% CI, −1.96 to −1.56; P <.00001).[17] Furthermore, lactulose was associated with significantly reduced blood ammonia levels (WMD: −9.89 mmol/L; 95% CI, −11.01 to −8.77 mmol/L; P <.00001).[17]

Lactulose administration can be complex due to the need for patients to self-titrate to achieve 2 to 3 bowel movements per day. A common effect of poor self-titration is over-use of lactulose, which can result in dehydration and hyponatremia—conditions that worsen or precipitate HE.[7] The Cochrane review found that AEs associated with lactulose included diarrhea, nausea, bloating, and flatulence.[16] In other studies, diarrhea was the most common AE related to lactulose treatment.[17] Patients with HE are susceptible to lactulose dehydration caused by over-diuresis, decreased oral intake secondary to anorexia, and diarrhea from infections or other medications.[18] In a retrospective study of 56 patients taking lactulose after an episode of HE, 8% of patients developed recurrent HE due to lactulose dehydration, defined as at least 5 bowel movements per day and accompanying azotemia (increased serum creatinine).[18]

Polyethylene Glycol 3350

Polyethylene glycol 3350–electrolyte solution (PEG) induces an osmotic effect that leads to water retention in the colon, causing watery stools.[19] PEG may benefit patients with cirrhosis who have been hospitalized for acute HE. PEG was compared with lactulose in the Hepatic Encephalopathy: Lactulose vs Polyethylene Glycol 3350-Electrolyte Solution (HELP) trial. A total of 50 patients with cirrhosis who were hospitalized for HE were randomly assigned to receive lactulose or PEG. Improvement was monitored by change in Hepatic Encephalopathy Scoring Algorithm (HESA) score, which ranges from 0 (normal clinical and neuropsychological assessments) to 4 (coma). Compared with patients receiving lactulose, a higher rate of patients receiving PEG improved by at least 1 HESA score (52% vs 91%; P <.01). Furthermore, the median time to HE resolution was shorter for patients receiving PEG compared with lactulose (1 vs 2 days; P = .01) (**Table 2**) [20] No treatment-related severe AEs were noted in either the PEG group or the lactulose group, and both therapies were considered safe. Nonetheless, the AASLD/EASL guidelines do not recommend PEG as a treatment for HE currently, citing the need for more studies.[3]

Antibiotics

Antibiotics, which were historically used to treat HE, include neomycin, metronidazole, oral vancomycin, and rifaximin. The efficacy and safety of these antibiotics as treatment options for HE have been investigated.

Neomycin

Based on evidence of an unfavorable risk–benefit profile, the 2014 AASLD/EASL practice guidelines recommend neomycin as an alternative treatment.[3,15] As early as 1977, neomycin was shown to

TABLE 2. HELP Trial Key Outcomes of Lactulose Versus PEG in Patients With Cirrhosis Hospitalized With HE[20]

Outcomes	Lactulose (n = 25)	PEG (n = 25)	P
Improved by:			
1 HESA grade, n (%)	9 (36%)	10 (43%)	
2 HESA grades, n (%)	3 (12%)	9 (39%)	
3 HESA grades, n (%)	1 (4%)	1 (4%)	
No improvement, n (%)	12 (48%)	2 (9%)	
24-hour HESA score change from baseline, mean (SD)	0.7 (0.8)	1.5 (0.8)	.002
Length of hospital stay, days, mean (SD)	8 (12)	4 (3)	.07
Median time to HE resolution, days	2	1	.01

6- to 24-hour ammonia, μmol/L, mean (SD)	Lactulose (n = 15)	PEG (n = 18)	P
Baseline	175 (70)	146 (75)	.19
6- to 24-hour follow-up	82 (29)	120 (60)	.049

HE indicates hepatic encephalopathy; HELP, Hepatic Encephalopathy: Lactulose vs Polyethylene Glycol 3350-Electrolyte Solution; HESA, Hepatic Encephalopathy Scoring Algorithm; PEG, polyethylene glycol 3350-electrolyte solution.

FIGURE 1. Phase 3 Efficacy Outcomes for Rifaximin Compared With Placebo for OHE Secondary Prophylaxis[25,a]
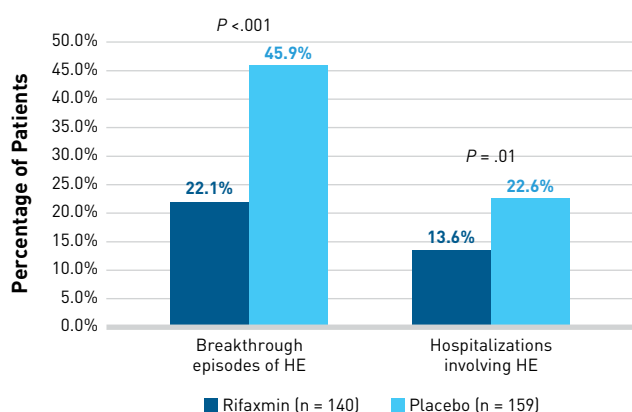
HE indicates hepatic encephalopathy; OHE, overt hepatic encephalopathy.
[a]Hospitalization with HE diagnosis or hospitalization during which an episode of HE occurred.

be noninferior to lactulose in an analysis of treatment efficacy in 33 patients with HE. When compared with lactulose, the efficacy rate (as measured based on a composite score of mental state, electroencephalography, and serum ammonia concentration) of neomycin treatment was similar (83% vs 87%; not significant).[21] Common AEs associated with neomycin include intestinal malabsorption, nephrotoxicity, and ototoxicity.[21,22] For treatment of

an acute episode of overt HE, previous studies used the dosing schedule of 1000 mg of neomycin every 6 hours for up to 6 days.[22]

Metronidazole
Metronidazole is an alternative option for short-term treatment of OHE, but the serious AEs associated with long-term use limit its utility for continuous treatment. These AEs include effects of ototoxicity, nephrotoxicity, and neurotoxicity, which may be exacerbated by the prolonged rate of elimination in HE patients.[3,22] When metronidazole was compared with neomycin in patients with mild to moderate severity HE, a similar efficacy profile was observed over 1 week. For this reason, other options with better safety profiles should be selected for management of acute episodes or for chronic HE.[3] For treatment of an acute episode of HE, studies have used the dosing schedule of 250 mg of metronidazole twice daily for 1 week.[22]

Vancomycin
Similar to neomycin and metronidazole, vancomycin is no longer commonly used as a first-line agent and is not even discussed in the 2014 guidelines.[22] In an investigation into the efficacy of vancomycin in patients with HE who were nonresponsive to lactulose, 2 to 3 days of vancomycin significantly improved the mean HE grade from baseline (2.0 vs 0.2; P <.001), with most cases of HE (n = 10/12) resolving completely.[23] Patients were continued on vancomycin for 8 more weeks before entering a crossover period, during which patients received lactulose or vancomycin for 8 weeks before crossing over to the other agent for 8 weeks. The crossover period revealed that mental status deteriorated in patients after crossing over to lactulose; however, in patients who were switched back to vancomycin, mental status improved.[23] Although vancomycin is safer for the management of HE than metronidazole or neomycin, vancomycin has fallen out of favor due to limited studies, high cost, and increased prevalence of vancomycin-resistant enterococci.[22]

Rifaximin
Rifaximin is a semi-synthetic derivative of rifampin and binds to the β-subunit of bacterial DNA-dependent RNA polymerase, blocking transcription and inhibiting bacterial protein synthesis.[24] In a phase 3 trial, rifaximin (n = 140) was compared with placebo (n = 159) as secondary prophylaxis in patients who were in remission from recurrent HE. Patients received treatment for up to 6 months or until a breakthrough episode of HE occurred.[25] Compared with placebo, significantly fewer breakthrough episodes occurred in the rifaximin group (22.1% vs 45.9%; HR, 0.42; 95% CI, 0.28-0.64; P <.001). Rifaximin also resulted in a 50% reduced risk of hospitalization compared with placebo (13.6% vs 22.6%; HR, 0.50; 95% CI, 0.29-0.87; P = .01) (**Figure 1**[25]). The numbers of patients needed to treat over a 6-month period to prevent 1 breakthrough episode or 1 hospitalization were 4 patients and 9 patients, respectively.[25] Because more than 90% of

patients continued on concomitant lactulose therapy, in actuality, patients were either taking rifaximin with lactulose, or placebo with lactulose. Therefore, the fewer breakthrough episodes of HE and reduced risk of hospitalizations in the rifaximin arm may provide benefits over lactulose therapy alone. The incidence of total AEs was similar between the rifaximin (80.0%) and placebo groups (79.9%). Common AEs included nausea, diarrhea, fatigue, peripheral edema, ascites, dizziness, and headache (**Table 3**).[25] The similar incidences of AEs between these 2 groups may be attributed to lactulose therapy, which most patients were taking. Therefore, rifaximin may have a favorable safety profile because rifaximin with lactulose therapy had AEs similar to those of lactulose therapy alone.

Rifaximin may also reduce the rate of hospitalization related to HE. In a small retrospective study of patients who received rifaximin (n = 15) or lactulose (n = 24) after a bout of stage 2 HE, the rates of hospitalization were evaluated.[26] Compared with lactulose, rifaximin was associated with a lower number of hospitalizations (19 vs 3 hospitalizations) and a shorter mean length of stay (5.0 vs 3.5 days; P <.0001)[26] Similarly, secondary prophylaxis with rifaximin was associated with fewer mean hospitalizations per patient compared with lactulose (0.5 vs. 1.6; $P \leq$.001) and fewer mean days of hospitalization (2.5 vs. 7.3; P <.001) (**Table 4**).[27]

The long-term safety and efficacy of rifaximin were investigated in a 24-month open-label study of patients with a history of recurrent OHE and at least 1 bout of OHE within 1 year of enrollment. Participants were included from an earlier randomized controlled trial of rifaximin, from which historical outcomes for placebo and rifaximin groups were drawn. The rates of AEs during long-term administration of rifaximin did not increase from historical rates. The event rate for serious AEs per person-year of exposure was lower for patients who received rifaximin compared with historical rates for patients who received placebo (0.48 vs 1.37 per person-year of exposure).[28] Similarly, the rate of mortality was similar between patients treated with rifaximin and historical placebo levels (0.15 vs 0.24 per person-year of exposure).

Several studies have investigated the efficacy and safety of rifaximin compared with other treatments for HE, including non-absorbable disaccharides and other antibiotics. In a meta-analysis of 12 studies, rifaximin led to modestly better clinical outcomes (complete resolution of HE or improvement of HE) compared with nonabsorbable disaccharides and lactulose (odds ratio [OR] = 1.96; 95% CI, 0.94-4.08; P = .07).[29] Common overall AEs included severe diarrhea, abdominal pain, nausea, vomiting, and weight loss. When all the AEs were pooled and compared between patients who received rifaximin (n = 908) or other agents (n = 988), patients who received rifaximin had a significantly lower risk of diarrhea (OR, 0.20; 95% CI, 0.04-0.92; P = .04). Furthermore, combined analysis of all AEs revealed a favorable safety profile with rifaximin use (OR, 0.27; 95% CI, 0.12-0.59; P = .001).[29]

TABLE 3. Common AEs in a Phase 3 Clinical Trial Comparing Rifaximin With Placebo for OHE Secondary Prophylaxis[25]

Rates of common AEs[a]	Rifaximin, n (%) N = 140	Placebo, n (%) N = 159
Nausea	20 (14.3%)	21 (13.2%)
Diarrhea	15 (10.7%)	21 (13.2%)
Fatigue	17 (12.1%)	18 (11.3%)
Peripheral edema	21 (15.0%)	13 (8.2%)
Ascites	16 (11.4%)	15 (9.4%)
Dizziness	18 (12.9%)	13 (8.2%)
Headache	14 (10.0%)	17 (10.7%)

AE indicates adverse event; HE, hepatic encephalopathy; OHE, overt hepatic encephalopathy.
[a]AEs occurring at an incidence rate of 10% or higher in the rifaximin group. The incidence of AEs did not differ significantly between groups (P <.05 for all comparisons).

TABLE 4. HE-Related Hospitalization Outcomes of Patients Treated With Rifaximin or Lactulose as Secondary Prophylaxis Following OHE[27]

	>6 months of treatment	
	Lactulose-treated patients	Rifaximin-treated patients
Mean number of hospitalizations	1.6	0.5
Mean days per hospitalization	7.3	2.5
Total time hospitalized	1.8 weeks	0.4 weeks
Estimated hospitalization charges per patient (per 6-month period)[a]	$56,635	$14,222

HE indicates hepatic encephalopathy; OHE, overt hepatic encephalopathy.
[a]Hospitalization charges were estimated based on average cost per hospital day in 2005 US dollars.

Rifaximin has been evaluated in combination with other agents, particularly for patients at high risk for recurrent OHE. In a randomized controlled trial evaluating lactulose with or without rifaximin, investigators reported that combination therapy increased the rate of complete HE reversal (76.0% vs 50.8%; P <.004), reduced the mean length of hospital stays (5.8 vs 8.2 days; P = .001), and decreased mortality (23.8% vs 49.1%; P <.05). Furthermore, more deaths due to sepsis were reported in the lactulose monotherapy group compared with combination therapy (17 vs 7 deaths; P = .01).[30] To reduce the risk of another recurrence, the AASLD/EASL 2014 guideline recommends adding rifxaimin to lactulose for ongoing management after an overt HE recurrence on lactulose alone.[3]

Other Options for Management of HE

Patients with previous bouts of HE or who have multiple risk factors should be advised about appropriate nutrition, which is an important part of nonpharmacologic management of HE. Historically, protein

restriction was recommended for patients based on the observation that high protein intake led to worse HE in 35% of patients with cirrhosis. Compared with healthy patients, however, patients with HE frequently suffer from moderate to severe protein calorie malnutrition due to accelerated fasting metabolism.[3] Muscle tissue plays an important role in the body's nitrogen metabolism, and muscle loss is associated with an increased risk of HE; therefore, protein requirements should be adjusted based on a patient's nutritional status, severity of HE, and hepatic reserve.[31] Daily protein intake of 1.2 to 1.5 g/kg per day is recommended in the 2014 AASLD/EASL guidelines for HE.[3] Protein intake will ideally be spread throughout the day into small meals followed by a nighttime snack of complex carbohydrates to reduce protein utilization. In a study evaluating nutrition habits of patients with HE, nighttime supplementation of protein was associated with increased total body protein stores compared with daytime feedings. For patients who find it difficult to consume the full volume of supplements, branched chain fatty acids can be considered.[15]

Sodium Benzoate and Sodium Phenylacetate
Sodium benzoate and sodium phenylacetate have been shown to enhance ammonia metabolism, suggesting a potential role for these agents in the treatment of HE. In a small study of sodium benzoate, an oral dose of sodium benzoate of 5 g twice daily was as effective as lactulose in lowering serum ammonia and improving cognition. However, usage has been limited due to gastrointestinal AEs, nausea, and limited clinical trials.[32]

Zinc
Among patients with cirrhosis and patients with alcohol-induced liver injury, zinc is often deficient. In small studies, zinc supplementation has been shown to decrease serum ammonia levels and alter neurotransmitter levels in the brain.[32] Zinc replacement can be considered for patients with HE using OTC supplements.

Probiotics
Probiotics alter colonic flora, which decrease urease-producing bacteria and promote growth of non–urease-producing bacteria. Studies have shown that *Enterococcus faecium* was comparable with lactulose in reducing ammonia levels and improving mental status in patients with chronic HE. In 1 such pilot study, probiotics improved cognitive function in 50% of patients with minimal HE. The probiotic Visbiome (De Simone Formulation) has been studied in multiple clinical trials and tested in more than 750 patients. In a small group of patients who consumed the De Simone Formulation, patients experienced a reduced incidence of HE, reduced ammonia levels, and improvements in psychometric tests when compared with the control group. Although probiotics may offer some potential benefits, probiotics are not frequently used because of the reluctance to introduce live bacteria into patients who have immunosuppressive conditions.[33]

Guideline Recommendations for the Management of HE
The diagnosis of HE is currently one of exclusion. The 2014 clinical practice guidelines for the diagnosis and management of HE developed by the AASLD/EASL recommend that clinicians should consider other causes of cognitive impairment, including diabetic pathologies, psychiatric disorders, or dementia. The guidelines do not currently recommend serum ammonia testing, as it does not add any diagnostic, staging, or prognostic value in assessing patients for HE.[3] The recommendation from the AASLD/EASL guidelines is based on the documented disparity between ammonia levels and HE severity in some patients with cirrhosis. In 10% of patients with HE, ammonia levels are normal, while ammonia levels are elevated in as many as 69% of patients without any symptoms of HE.[34] Although ammonia plays a critical role in HE pathogenesis, the discrepancies between serum ammonia and HE symptoms reveal the contributory roles of other factors in HE, including cytokine storms related to systemic inflammation, which may have synergistic effects with the impaired nitrogen metabolism.[35]

The site of care and treatment for HE are dependent on the severity of the condition. Outpatient community care is typically sufficient for patients with CHE. No blanket recommendations for CHE treatment exist; however, the documented impact of CHE on quality of life, work performance, driving ability, and overall survival may underscore the importance of appropriate management.[8] Hospitalization with follow-up prophylaxis is typically reserved for patients with OHE, who may need management of the underlying cause of OHE (eg, gastrointestinal bleeding or infection) in addition to the provision of pharmacologic therapy that reduces ammonia production.[6]

For spontaneous or precipitated cases of OHE type C, lactulose is usually the first choice of treatment. Rifaximin is considered an effective add-on therapy and may be used in combination with lactulose for the prevention of OHE recurrence. Although the safety profiles tend to be unfavorable, neomycin and metronidazole are alternate treatment options for OHE. If patients have both recurrent intractable OHE and liver failure, they are indicated for liver transplantation.[3]

Early prevention is often a priority in HE management and can be started in the inpatient setting. Primary prophylaxis for prevention of OHE is recommended for patients with cirrhosis who have a high risk of developing HE. Secondary prophylaxis is recommended for most patients after an episode of OHE. The guidelines recommend continued, indefinite treatment in this patient population based on the hypothesis that once the threshold for OHE is reached, patients are at a high risk of recurrence. In some circumstances, such as when the precipitating factors have been improved (eg, in the case of infections or variceal bleeding), prophylactic therapy may be

discontinued. Although TIPS can be a precipitating factor for HE, routine prophylactic therapy is not recommended following TIPS in the absence of other risk factors.[3]

Socioeconomic Burden of HE

The economic burden associated with HE is substantial and currently increasing. From 2005 to 2009, the total charges for hospitalizations associated with HE increased by 55.1%. Hospitalizations related to HE accounted for approximately 0.33% of all hospitalizations in the United States, with the average length of stay increasing from 8.1 days in 2005 to 8.5 days in 2009. Total hospitalization charges for patients with HE, including resource utilization, number of inpatient procedures, and average length of stay, increased from $4.68 billion in 2005 to $7.25 billion in 2009.[10] Furthermore, from 2005 to 2009, 2.7% more patients were transferred to long-term care or nursing facilities after hospitalization. These growing rates of transfers to outside facilities not only increase overall costs, but also reflect the morbidity outcomes that follow patients with HE after hospital discharge.[10]

The cost burden of HE frequently falls on the federal government through the Medicare and Medicaid programs. According to national statistics from 2002, 71% of patients with HE had Medicare or Medicaid insurance, 22% had private insurance, and 7% were uninsured or had other forms of payment.[5] Furthermore, patients with Medicare and Medicaid had a 7% to 8% increased length of hospitalization stay and up to 2.4% higher costs incurred, indicating a higher level of resource use among Medicaid and Medicare patients with HE.[1]

Patients with both CHE and OHE are often burdened by indirect economic costs of HE associated with an inability to work and lost wages. Compared with patients with cirrhosis but no HE, patients with previous HE had a higher rate of unemployment (87.5% vs 19%; *P* = .0001), were more likely to report that their financial status was worse since the diagnosis of cirrhosis (85% vs 61%; *P* = .019), and were more likely to need to decrease their time spent working (71% vs 39%; *P* = .017) (**Figure 2**).[36] Even for patients with MHE, unemployment rates are relatively high. Approximately 50% of patients with MHE are unemployed compared with 15% of patients with cirrhosis alone.[37]

Quality of life is also reduced among patients with HE. Patients with cirrhosis and HE have deficiencies in most measures of quality of life, with the most notable impairments in social interaction, alertness, emotional behavior, mobility, sleep/rest, work, home management, and recreation and pastimes.[38] Among patients with MHE, impairments are most common in mental health components of the Short Form–36, which measure emotional role functioning, vitality, mental health, and social factors.[38] Furthermore, previous bouts of HE that have been resolved may still impact the mental health of patients, with prior HE significantly correlating with the mental component score of the Short Form–36 in a study of patients with cirrhosis (*P* = .03).[39] Moreover, the ability to safely operate a vehicle

FIGURE 2. Comparison of Self-Reported Financial Status of Patients With Cirrhosis With and Without Previous Bouts of Resolved HE[36]
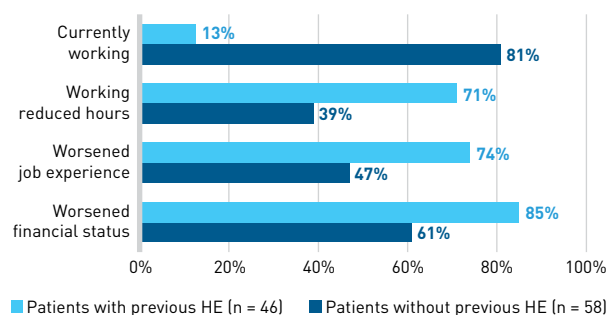
HE indicates hepatic encephalopathy.

may be reduced in patients with MHE. Car handling, following road signals, following traffic laws, and paying attention to pedestrians and cyclists were all reduced among patients with MHE. In some states, physicians are required to report patients with HE to the state motor vehicle association so that their driver's licenses may be revoked.[38]

Caregivers and families of patients with HE also experience substantial burdens related to the financial, emotional, physical, and time-commitment strains of HE. Families of patients with HE reported that they needed to stop saving money to pay for medical costs (56%), were in debt (46%), or became bankrupt (7%) after the initial cirrhosis diagnosis.[36] When compared with caregivers of patients with cirrhosis alone, caregivers of patients with HE have a greater total caregiver burden due to factors associated with finances, schedule, personal health, and feelings of entrapment.[36] Caregivers of patients with HE also suffered from higher rates of depression and anxiety compared with caregivers of patients with cirrhosis alone. A total of 18% of caregivers of patients with HE had mild depression, and 5% had severe depression. Similarly, 22% of caregivers had mild anxiety, and 5% had severe anxiety.[36]

Adherence to HE Treatment

Effective HE management is reliant on patient adherence to treatment. In a retrospective analysis of 137 patients with cirrhosis who received secondary prophylaxis for HE, the association of adherence and recurrence was evaluated. Of the 103 patients who developed recurrent HE (75.2%), 39 patients (38%) were non-adherent to their lactulose prescription, which was measured by patient questioning, family questioning, and inconsistent refills based on electronic pharmacy records.[18] Furthermore, all patients who did not have HE recurrence were adherent to lactulose, while those with recurrent HE had adherence rates of 64% (*P* = .00001).[18] In a study of 402 patients discharged after cirrhosis-related complications, 22% of hospital readmissions that occurred within the first month were considered preventable through patient education on the proper use

and maintenance of lactulose treatment, highlighting the importance of adherence and the role of the clinician in improving adherence.[40]

Poor adherence rates may contribute to the cost burden associated with HE. In a study analyzing hospitalizations pertaining to HE recurrence, it was found that 40% of HE recurrences were due to lactulose noncompliance and 8% were due to lactulose overuse.[41] As stated earlier, in 2009, the US incidence of HE was reported to be 115,814, with approximately 98,673 (85.2%) of hospitalized patients with major or extreme disease severity. Using data from 2009, the average hospitalization associated with HE costs $17,812 per patient. According to a study analyzing a retrospective medical record review, 40% of HE reoccurrences were attributed to lactulose noncompliance.[42] If 40% of those 98,673 hospitalized patients were hospitalized due to lactulose noncompliance, then an estimated cost of $703 million was associated with lactulose noncompliance.[1,42] If 8% of those 98,673 hospitalized patients were hospitalized due to lactulose overuse, then an estimated cost of $141 million was associated with lactulose overuse.

Several studies have demonstrated high rates of adherence with rifaximin. In a 6-month safety and efficacy study of rifaximin among patients with recurrent HE, the rates of adherence, defined as the use of 80% or more of dispensed tablets, were considered good in both the rifaximin group (n = 140; 84.3%) and the placebo group (n = 159; 84.9%).[25] Similarly, in a study of 42 patients with MHE, adherence to rifaximin was 92%, with only 2 patients taking less than 80% of the study drug.[43] When compared with lactulose in a retrospective chart review of 145 patients with HE, the rates of adherence, defined as taking 75% or more of the prescribed doses, were significantly higher in the rifaximin group (31% vs 92%; *P* <.001).[27]

The AEs associated with treatment may impact adherence rates. Gastrointestinal AEs are common among patients taking lactulose and include bloating, abdominal pain, diarrhea, flatulence, cramping, nausea, and anorexia.[7,15] Additionally, the dosing schedule can be complex and may affect treatment adherence. Lactulose is prescribed at a dose intended to achieve 2 to 3 bowel movements per day, but self-titration following discharge may be necessary to achieve the appropriate frequency.[7,18] Self-titration can be unclear and difficult for patients and they have trouble with the self-titration process. Adherence of patients to self-titration with lactulose was evaluated and analyzed relative to the time since the index episode. Patients were more adherent immediately following their first bout of HE and became less adherent over time, as indicated by a lack of self-titration to achieve 2 to 3 bowel movements per day. These data highlight the complexity of self-titrating lactulose and managing AEs.[18]

Cost Considerations for the Management of HE

The economic burden of HE is substantial and is expected to increase given the rising direct costs of hospitalizations, outpatient care, and HE treatment in the United States. Reducing the rate of HE-related hospitalizations is an important measure which has the ability to reduce total cost of HE management. Additionally, the indirect costs of lost working time and productivity also contribute to the financial burden of this disease.

HE is the most common cause of readmission in patients with cirrhosis and is a driver of 30-day and 90-day readmission risks. In an analysis of payer administrative datasets from the Healthcare Cost and Utilization Project for 6 states in the United States, patients with index hospital admissions for cirrhosis (N = 119,722) were analyzed for readmission rates and cause of readmission. The presence of HE in these patients was most strongly associated with readmission within 30 and 90 days compared with any other cirrhotic complication, infection, or renal injury (unadjusted OR, 1.64; 95% CI, 1.56-1.72). Readmissions rates for HE were 18.1% for 30-day readmissions and 28.8% for 90-day readmissions.[44] Additionally, of patients without HE at index hospitalization (N = 13,679), 9.7% were readmitted within 30 days with HE as an active complication. In 43.6% of the patients readmitted, HE was the primary billing diagnosis, indicating the large economic burden associated with HE in repeat hospitalizations.[44]

In a study of 2075 patients with index cirrhosis-related hospital admissions to a community hospital and 2 regional hospitals over nearly 3 years, 655 patients were readmitted within 30 days of hospitalization. This translated to an overall readmission rate of 32%, and HE-related readmissions within 30 days of hospitalization accounted for 13.6% of all readmissions. Of the 157 readmissions within 30 days to the community hospital, the most common readmission was for HE without obvious infection and ascites or its complications in 29.5% of patients.[45] HE was the primary reason for 30-day readmission in 8.6% of the 498 patients readmitted to regional hospitals. In an analysis of hospital readmission costs in this study population with cirrhosis, patients who were not readmitted following index hospitalization had posthospitalization outpatient costs totaling $5719 per patient. The population of patients readmitted within 30 days of hospitalization had the highest overall postindex costs (including outpatient and hospitalization costs following index hospitalization) of $73,252 per patient compared with $62,053 per patient for those readmitted after 30 days following the index hospitalization.[45]

Reducing the risk of early hospital readmissions is important to the cost-effective management of HE. As up to 40% of hospital readmissions for HE are preventable with appropriate lactulose and rifaximin combination treatment,[41] the burden of hospitalization rates in this population can be improved with effective management.[46] The potential cost savings of rifaximin prophylaxis in the prevention of repeat hospitalizations for patients with HE can be estimated by extrapolating data on hospitalization outcomes from the phase 3 trial presented earlier (Figure 1).[25] As stated previously, an estimated 85.2% of the US population with HE, or 98,673 Americans, were hospitalized with major or extreme disease severity in 2009. Assuming that all patients with major or extreme

HE graded disease severity were treated with rifaximin in 2009, hospitalization readmissions within 6 months would occur in 13,420 patients for a repeat OHE episode (13.6%).[25] If all patients were not treated with rifaximin, hospitalization would occur in 22,300 patients (22.6%) within 6 months. As discussed, the average inpatient hospitalization cost associated with HE was estimated at $17,812 per patient in 2009. With rifaximin treatment, there would be an estimated decrease of 8880 hospitalizations, which translates to approximately $158 million saved on hospital readmission for HE in 6 months compared with no rifaximin treatment.[1,25]

Quality improvement programs are designed to reduce readmission risk and offer more effective treatment to patients with HE. Lower 30-day readmission risk for HE was demonstrated when implementing a quality improvement program using electronic decision support (default ordering of treatments at the point of care) for clinicians for improved uptake of higher dose and frequency of lactulose and routine use of rifaximin for OHE.[44,46] Implementing quality improvement programs also requires business planning for costs and cost effectiveness of an intervention, including competitive analysis with available alternatives.[46]

Cost-effective analysis of agents used in the management of HE was conducted using a model developed from the perspective of a third-party payer in the United States. This model was designed to account for direct costs of medications and hospitalization as well as indirect costs, cirrhosis-related costs (eg, ascites, liver transplantation, outpatient care), and nonmedication costs (eg, doctor visits, laboratory tests). The model assumed that the population was for patients with 50% subclinical HE and 50% OHE. The following 6 treatment strategies were considered in the model for patients naïve to treatment for HE: no treatment, lactulose monotherapy, lactitol monotherapy, neomycin monotherapy, rifaximin monotherapy, and lactulose with crossover to rifaximin if the patient could not tolerate lactulose or had poor response (rifaximin salvage).[47] Of the 6 treatment options, lactulose monotherapy and rifaximin salvage therapy were most balanced in outcomes; these treatments were less expensive and more effective. Although lactulose monotherapy was the least expensive treatment, with $56,967 in the total lifetime combined cost of care, rifaximin salvage was the most effective treatment option, with 6.9 life-years and 5.3 quality-adjusted life-years gained from treatment.[47]

In a retrospective review of 39 patients with HE treated with lactulose or rifaximin from January 2004 to November 2005, secondary prophylaxis with rifaximin reduced the number of hospitalizations and length of hospital stays in patients with previous OHE compared with lactulose treatment.[5,26] Reduced rates of hospitalization and emergency department (ED) visits from rifaximin treatment were related to lower overall total cost of therapy compared with lactulose. Aggregating the costs of hospitalizations, ED visits, and drug costs, the mean total cost of therapy for patients treated with lactulose was $13,285 per patient compared with $9958 per patient treated

FIGURE 3. Rifaximin Compared With Lactulose Based on Retrospective Chart Review of Patients With OHE[5]
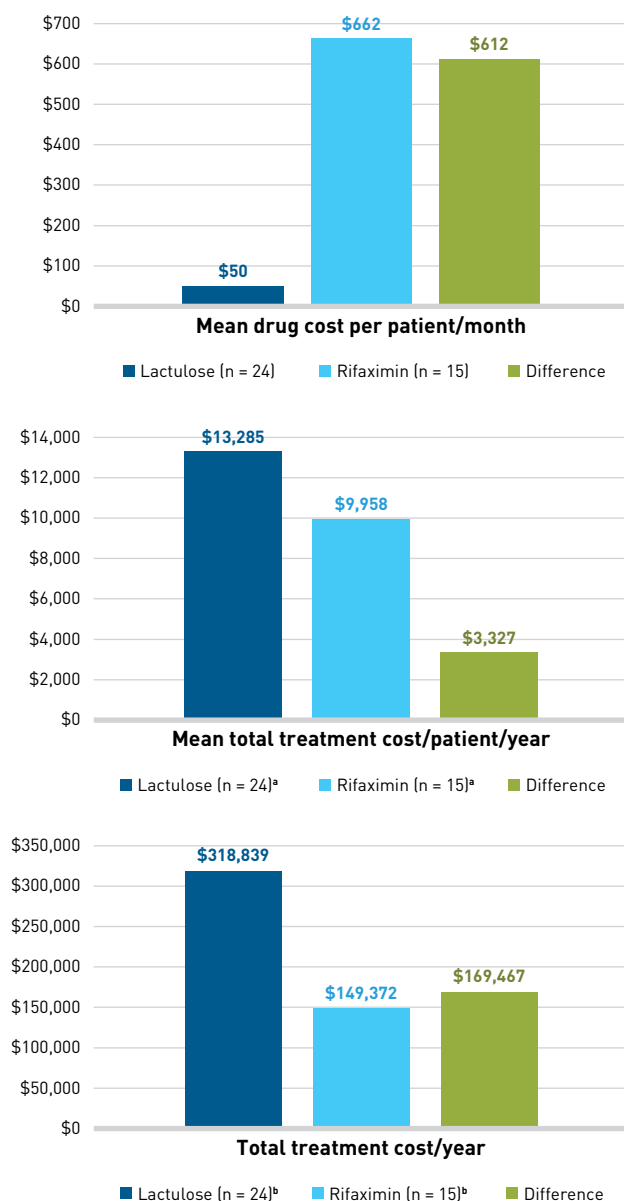
OHE indicates overt hepatic encephalopathy.
[a]Includes annual drug costs, hospitalizations, and emergency department visits for 19 lactulose group hospitalizations and 3 rifaximin group hospitalizations.
[b]Extrapolated from all patients.
[c]Listed charges of rifaximin are from the 200-mg formulation. When compared on a mg-to-mg basis, the current 550-mg formulation is less expensive than the 200-mg formulation.

with rifaximin. Treatment with rifaximin resulted in a mean cost difference per patient of $3327 compared with lactulose.[5] Using data extrapolated from this study, if all 39 patients enrolled selected rifaximin treatment over lactulose, this group would have total savings of nearly $170,000 per year (**Figure 3**).[5]

Indirect costs, such as physician office visits and drug compliance, were not analyzed in this study. These excluded indirect costs suggest that rifaximin may offer potentially greater cost savings than calculated in this analysis.[5] This study utilized charges associated with the 200-mg formulation of rifaximin in the cost of therapy assessments, where the drug cost of rifaximin is more expensive than the drug cost of lactulose ($662 vs $50, respectively).[5] Notably, when directly comparing mg-to-mg costs, the 550-mg formulation of rifaximin is less expensive than the 200-mg formulation. As this 550-mg formulation was not accounted for in the analysis, rifaximin has the potential to offer savings additional to those demonstrated in this study.

In a study of 145 patients who received at least 6 months of lactulose followed by at least 6 months of rifaximin, HE treatment cost outcomes from the lactulose and rifaximin treatment periods were compared. Compared with the rifaximin treatment period, hospital charges exceeded $42,000 more per patient during the lactulose period ($56,635 vs $14,222). This difference in cost was likely attributed to fewer incidences of hospitalizations and shorter lengths of hospital stay.[27]

Conclusions

Cost-effective management of HE is essential, as the combined direct and indirect medical costs of this condition represent a large economic burden for individuals, healthcare systems, and society. Additionally, OHE is often recurrent, and each episode contributes to the overall burden of this disease. Although CHE does not typically require hospitalization, patients living with this condition may still experience associated quality-of-life reductions caused by neurocognitive and physical decline. Regarding the economic burden of medications, studies have shown that rifaximin in combination with lactulose may be a cost-effective treatment option that reduces hospitalizations and improves adherence to maintenance therapy.

According to the 2014 AASLD/EASL practice guidelines for HE in chronic liver disease, rifaximin is recommended as an effective add-on therapy for the prevention of recurrence of OHE is patients treated with lactulose. Alternative options include PEG and antibiotics such as neomycin, metronidazole, and vancomycin. While these agents have been historically used for HE treatment, they have fallen out of favor due to limited recent studies and a relatively poor risk–benefit profile. At present, rifaximin therapy appears to offer greater potential efficacy, safety, and cost benefits when compared with lactulose through its associated reduction in hospitalizations, enhanced patient quality of life, and improved adherence attributable to a favorable AE profile. ∎

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