Management of Hepatic Encephalopathy in the Hospital

Michael D. Leise, MD; John J. Poterucha, MD; Patrick S. Kamath, MD; and W. Ray Kim, MD

Abstract

Hepatic encephalopathy (HE) develops in up to 50% of patients with cirrhosis and is a feature of decompensated cirrhosis. With the goal of reviewing the evidence for treatment and prevention of overt hepatic encephalopathy, pubmed was searched using search terms hepatic encephalopathy AND treatment, limited to human studies from January 1, 2003, through December 1, 2013, and supplemented by key references. The inpatient incidence of HE is approximately 23,000 annually, and management of these patients is common for internists and subspecialists. Treatment of the hospitalized patient with HE has changed in recent years. Treatment entails 2 phases: induction and maintenance of remission. Most cases of significant HE are precipitated by infection, gastrointestinal bleeding, medications, or other culprits. All patients should be evaluated for secondary triggers of HE, and treatment should be initiated with a nonabsorbable disaccharide (ie, lactulose) in most patients. Rifaximin (off label) can be added in patients not responding to lactulose. Neomycin is a less preferred alternative to rifaximin owing to its adverse effect profile. Other therapies, including zinc, L-ornithine–L-aspartate, and branched-chain amino acids, can be considered for patients not responding to disaccharides and nonabsorbable antibiotics. Large portosystemic shunts may be embolized in patients with medically refractory recurrent or severe HE with otherwise well-compensated cirrhosis. Molecular Adsorbent Recirculating System is now available for patients with severe HE who do not respond to medical therapy. It is critically important that patients hospitalized with significant HE continue maintenance therapy at the time of dismissal to prevent further episodes. Patients with a first-time episode of HE can be administered lactulose, and careful instructions should be provided to patients and caregivers about dose titration to achieve 3 bowel movements daily. Patients with recurrent HE episodes despite lactulose use benefit from the addition of rifaximin, which decreases the frequency of recurrent HE episodes and related hospitalizations. Last, patients and their families should be counseled about the risk of motor vehicle accidents, which require mandatory reporting to the Department of Motor Vehicles in some states.

Hepatic encephalopathy (HE) is a significant neuropsychiatric syndrome that most commonly occurs in decompensated cirrhosis. Clinical features range from clinically imperceptible symptoms in minimal HE (MHE), which require neuropsychometric testing to identify, to a comatose state in the worst cases.¹ The Working Party for Hepatic Encephalopathy established nomenclature for HE in 1998.² Type A HE refers to HE secondary to acute liver failure, type B refers to enteric hyperammonemia (without liver disease), and type C is associated with chronic liver disease. The severity of HE is graded using the WestHaven criteria (grades 1-4), but alternative terminology has been suggested and has gained some traction. In the new lexicon, called SONIC (spectrum of neurocognitive impairment in cirrhosis), covert HE (CHE) includes MHE and grade 1 HE and overt HE (OHE) encompasses grades 2 to 4 HE (Table 1). Episodic HE develops over a short time frame and can fluctuate, whereas persistent HE impairs day-to-day executive function. Most patients with episodic OHE (grade 2 or higher) will require management in the hospital, which is the focus of this review.

Hepatic encephalopathy eventually occurs in up to 50% of patients with cirrhosis.³⁴ Hepatic encephalopathy portends a worse survival for patients compared with similar patients without HE, even after accounting for the Model for End-Stage Liver Disease (MELD) score.⁵ The development of HE merits consideration of liver transplantation. Whether treatment of HE alters survival is unknown. Treatment of HE continues to be a significant area of investigation. Currently,
nonabsorbed disaccharides (eg, lactulose and lactitol) and nonabsorbable antibiotics (eg, neomycin and rifaximin) represent the mainstay of treatment (Table 2).

Hospitalization for episodic OHE, or the development of OHE during hospitalization, is common. In the US Nationwide Inpatient Sample, the inpatient incidence of HE ranged from 20,918 (in 2005) to 22,931 (in 2009).6 Up to 80% of OHE episodes are precipitated by an event such as infection or gastrointestinal bleeding. Management of the hospitalized patient with episodic OHE, common for internists and subspecialists, is directed at correcting the underlying precipitant and providing pharmacologic treatment that reduces ammoniagenesis.

Most patients require maintenance medications at the time of hospital dismissal as secondary prophylaxis for episodic OHE. Data suggest that many patients do not receive maintenance medication at or after dismissal. An abstract presented at the American Association of the Study for Liver Disease annual meeting in 2012 characterized a subset of insurance claims for patients by International Classification of Diseases, Ninth Revision code for HE (code 572.2) and compared this to prescriptions filled between January 1, 2009, and December 31, 2011. For 2009 (n=13,623), 2010 (n=15,529), and 2011 (n=16,328), 89.2%, 87.8%, and 86.4% of patients with HE had inpatient claims for HE, respectively, and 60.3%, 62.3%, and 63.9% did not receive ongoing treatment.7,8 Volk et al9 also described a high readmission rate (69%) in a cohort of patients with decompensated cirrhosis (n=402) where one of the most common reasons for preventable readmission was recurrent HE due to lack of education on or inappropriate use of lactulose. Thus, more attention should be focused on ensuring that patients are prescribed and educated about maintenance medication therapy for secondary prevention of OHE at the time of hospital dismissal.10 In this review, we summarize the evidence on the optimal medical treatments for patients who have been hospitalized for episodic OHE and suggest treatment algorithms.

### ARTICLE HIGHLIGHTS

- Episodic overt hepatic encephalopathy (OHE) is responsible for an increasing number of hospital admissions and readmissions.
- New terminology has been suggested and is gaining traction in which West Haven grades 0 and 1 are covert HE and grades 2 to 4 are OHE.
- Most patients with OHE require hospital-based care during the induction treatment phase, followed by a maintenance treatment strategy in the outpatient setting.
- Lactulose is the mainstay of induction and maintenance treatment.
- Rifaximin, when added to lactulose, has been found to prevent episodes of OHE and hospitalization compared with lactulose alone.
- Rifaximin and neomycin are acceptable adjunctive therapies for patients with OHE who are not responsive to lactulose or who have severe OHE, although rifaximin may be preferable owing to a better adverse effect profile.
- Evidence for the use of zinc, L-ornithine—L-aspartate, and branched-chain amino acids is less compelling, whereas there is increasing data to suggest a benefit of portosystemic shunt embolization in carefully selected patients.

#### TABLE 1. Hepatic Encephalopathy Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Intellectual Impairment</th>
<th>Neuromuscular Impairment</th>
<th>SONIC criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>MHE</td>
<td>Normal examination findings; subtle changes in work or driving</td>
<td>Minor abnormalities of visual perception or on psychometric or number tests</td>
<td>Covert</td>
</tr>
<tr>
<td>1</td>
<td>Personality changes, attention deficits, irritability, depressed state</td>
<td>Tremor and incoordination</td>
<td>Covert</td>
</tr>
<tr>
<td>2</td>
<td>Changes in sleep-wake cycle, lethargy, mood and behavioral changes, cognitive dysfunction</td>
<td>Asterixis, ataxic gait, speech abnormalities (slow and slurred)</td>
<td>Overt</td>
</tr>
<tr>
<td>3</td>
<td>Altered level of consciousness (somnolence), confusion, disorientation, amnesia</td>
<td>Muscular rigidity, nystagmus, clonus, Babinski sign, hyporeflexia</td>
<td>Overt</td>
</tr>
<tr>
<td>4</td>
<td>Stupor and coma</td>
<td>Oculocephalic reflex, unresponsiveness to noxious stimuli</td>
<td>Overt</td>
</tr>
</tbody>
</table>

MHE = minimal hepatic encephalopathy; SONIC = spectrum of neurocognitive impairment in cirrhosis.
for induction and maintenance of remission (secondary prophylaxis). Liver transplantation for HE is not covered in this review.

The search strategy used for this review included the search terms hepatic encephalopathy and treatment in PubMed, with filters of human and past 10 years. Bibliographies were also manually searched, as were abstracts from recent liver conferences. Clinical trials were emphasized when discussing evidence for each modality.

**EVIDENCE FOR INDUCTION THERAPIES TO TREAT EPISODIC OHE**

**Nonabsorbable Disaccharides**
Lactulose (β-galactosidofructose) and lactitol (β-galactosidosorbitol) reduce ammonia levels by acidification of the colon with resultant conversion of ammonia to ammonium, shifting the colonic flora from urease- to non-urease-producing bacterial species, and by their cathartic effect. Nonabsorbable disaccharides have demonstrated variable efficacy in clinical trials. An often-cited meta-analysis performed in 2004 found that nonabsorbable disaccharides were superior to placebo but did not improve survival.11 When only high-quality trials were included in this meta-analysis, nonabsorbable disaccharides had no effect on HE. To our knowledge, there have been no trials of nonabsorbable disaccharides vs placebo since these results. Despite the mixed results, lactulose still remains the first-line therapy for acute episodic OHE. Decades of clinical experience with lactulose speaks to its effectiveness to reverse episodic OHE in all but the most severe of cases. The discordance between efficacy in clinical trials and real-life effectiveness is manifold and includes heterogeneity in the types of HE (minimal vs overt vs chronic), differences in the prognostic importance of HE precipitants, and subjectivity of HE assessment tools. Clinical guidelines recommend lactulose or lactitol as first-line therapy.10

**Neomycin, Metronidazole, and other Antibiotics**

Neomycin is a poorly absorbed aminoglycoside used to decrease gut bacteria-derived ammonia, and it is Food and Drug Administration (FDA) approved for use in acute (episodic) OHE but not chronic HE. There are multiple older studies that explore the efficacy of this agent in HE. One of the earliest studies, by Atterbury et al12 in 1978, was a randomized controlled trial (RCT) comparing neomycin-sorbitol with lactulose in acute (episodic) HE that found no difference between the 2 therapies. One of the most recent studies, from 1992, compared neomycin, 6 g/d (n=20), with placebo (n=19) for episodic HE in a double-blind randomized trial and found no statistically significant difference in treatment failures (2 per group) or mean ± SD time to resolution of HE in the neomycin arm (39.11±23.04 hours) vs the placebo arm (49.47±21.92 hours).13 In general, the evidence for neomycin in episodic OHE is weak, and its use is complicated by the risk of ototoxicity and nephrotoxicity. Although neomycin is FDA approved, its decreased efficacy and adverse effects compared with other therapies limit its clinical utility. Other small trials have evaluated metronidazole and vancomycin and have suggested some benefit, but the risk of neurotoxicity and vancomycin-resistant enterococci colonization, respectively, hamper any enthusiasm about using these agents as mainstays in the armamentarium for HE.14-19

**Rifaximin**
The role of rifaximin in the treatment of episodic OHE is contentious. Rifaximin is not FDA approved for the treatment of episodic OHE, only for the secondary prevention of OHE. Older trials that evaluated rifaximin for episodic HE used different comparators and generally enrolled small numbers of patients with acute, chronic, or unclear acuity of HE. Bucci and Palmieri20 compared rifaximin (1200 mg/d) with fixed-dose lactitol (30 g/d) in 30 and 28 patients with moderate to severe HE, respectively. It was not clear whether these patients had OHE or chronic HE. End points were HE grade, neuropsychometric test results, and ammonia level at days 3, 6, 9,
TABLE 3. Disaccharides vs Rifaximin for the Treatment of HE: Summary of Trials

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Method</th>
<th>HE type</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bucci and Palmieri, 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>N=58 DB, RCT</td>
<td>Unknown</td>
<td>Rifaximin, 1200 mg; lactulose, 30 g</td>
<td>MS, asterixis, cancellation test, Reitan test, EEG, ammonia</td>
<td>Improvement in MS, ammonia level, cancellation test, EEG more pronounced, and faster onset with rifaximin</td>
</tr>
<tr>
<td>Festi, 1993&lt;sup&gt;26&lt;/sup&gt;</td>
<td>N=21 RCT, OL</td>
<td>Grade 1 HE</td>
<td>Rifaximin, 1200 mg; lactulose, 40 g</td>
<td>HE symptoms, ammonia, serum Na+</td>
<td>HE symptom improvement comparable; faster onset for asterixis, ammonia, Na+ in the rifaximin group</td>
</tr>
<tr>
<td>Massa, 1993&lt;sup&gt;27&lt;/sup&gt;</td>
<td>N=40 DB, RCT</td>
<td>Grade 2-3 HE</td>
<td>Rifaximin, 400 mg TID; lactulose 20 g TID</td>
<td>PSE Index</td>
<td>MS improvement favored rifaximin, as did ammonia level (faster drop), Reitan test, and earlier change in EEG</td>
</tr>
<tr>
<td>Mas 2003&lt;sup&gt;28&lt;/sup&gt;</td>
<td>N=103 DB, RCT</td>
<td>Grade 1-3 acute HE</td>
<td>Rifaximin, 1200 mg; lactitol, 60 mg (titrated)</td>
<td>PSE Index</td>
<td>Comparable overall global improvements in both groups (≥ 80%), with patients taking rifaximin demonstrating better HE grade, ammonia level, and EEG (statistically significant) and higher % with complete HE resolution (53% vs 37%)</td>
</tr>
<tr>
<td>Paik et al&lt;sup&gt;22&lt;/sup&gt; 2005</td>
<td>N=54 OL, RCT</td>
<td>Grade 1-3</td>
<td>Rifaximin, 1200 mg; lactulose, 90 ml</td>
<td>HE index, MS, asterixis, Reitan test</td>
<td>Improvements for both, no statistically significant difference for any outcome</td>
</tr>
</tbody>
</table>

DB = double blind; EEG = electroencephalogram; HE = hepatic encephalopathy; MS = mental status; Na+ = sodium; OL = open label; PSE = portosystemic encephalopathy; RCT = randomized controlled trial; TID = 3 times daily.

12, and 15. Overall, there did not seem to be any clinically important differences between groups at day 15 across all end points considered, but rifaxim did seem to result in faster improvement compared with lactitol. An RCT of rifaxim vs placebo for acute HE (grades 1–3) found improvement in a composite outcome (including mental status, neuropsychometric test results, electroencephalographic findings, and ammonia level) at doses of 1200 and 2400 mg/d. A randomized, double-blind, double-dummy, controlled trial compared rifaxim, 1200 mg (n=50), with lactitol, 60 g/d (n=53), and found approximately 80% efficacy in both arms after 5 to 10 days of treatment. An open-label randomized trial in Koreans compared rifaxim, 1200 mg (n=32), with lactulose, 90 ml/d (n=22), in OHE grades 1 to 3 and found no difference in improvement in HE grades or composite end points. Rifaxim was better tolerated in most studies, as anticipated. Table 3 summarizes data in trials comparing lactulose/lactitol with rifaxim that generally reported similar outcomes in both treatment groups. Given the small number of trials and their methodologic flaws, the question of using rifaxim as monotherapy for episodic OHE remains unanswered.

Rifaxim use for episodic OHE, in addition to lactulose use, has become increasingly common despite a previous lack of evidence. A recent RCT (n=120) was conducted by Sharma et al<sup>23</sup> comparing rifaxim and lactulose with lactulose and placebo in patients with OHE. Eighty percent of patients had severe HE, grade 3 or 4, and 70% were Child-Turcotte-Pugh class C, with the remainder Child-Turcotte-Pugh class B. Patients in the lactulose and rifaxim group had a higher proportion of complete reversal of HE (76% vs 50.8%, P<.004), shorter hospital stays, and a striking improvement in 10-day mortality (49.1% vs 23.8%, P<.05). The very high mortality rate in the lactulose plus placebo arm raises some concerns about the validity of this study, which should be repeated in a larger number of patients at multiple sites. In the meantime, this is likely the best data that will be available for some time with which to make evidence-based treatment decisions.

Zinc

Zinc deficiency is common in cirrhosis. In a recent clinical trial, the zinc deficiency prevalence was 96% in patients with a median MELD score of 12. Ammonia is converted to urea by ornithyl transcarbamylase in the liver and is combined with glutamate by glutamine synthetase in the skeletal muscle to form glutamine. Both ammonia-reduction pathways are impaired by zinc deficiency. Treatment with zinc has been found to enhance the formation
of urea from ammonia and amino acids.\textsuperscript{25} Zinc therapy has been the focus of 4 RCTs, producing heterogeneous results. Three of these trials are now 20 years old or more.\textsuperscript{20-31} The most recent study, from Takuma et al\textsuperscript{24} in 2010, randomized patients with cirrhosis and HE grades 1 and 2 refractory to standard treatment to receive zinc treatment (n=39) in addition to lactulose and branched-chain amino acids (BCAAs) vs no zinc (n=40) with BCAA and lactulose. Patients were followed for 6 months to determine the effect on quality of life and HE. Hepatic encephalopathy improved in 21 (54\%) vs 10 (26\%) of patients in the zinc vs no zinc arms, with 16 zinc-treated patients (41\%) improving to HE grade 0. Other end points, including ammonia level, psychometric test results, and quality of life, were met in the zinc treatment arm. Although this study had some flaws, including lack of blinding and the zinc formulation (contained \textit{L}-carnosine), it is the only recent study with reasonable evidence to suggest the benefit of zinc. There is not enough data to define the optimal dose of zinc. Zinc is relatively well tolerated, with rare adverse effects of dyspepsia and copper deficiency (with long-term, high-dose use), and can decrease the effectiveness of ciprofloxacin if taken at the same time (take zinc 2 hours before or 6 hours after taking ciprofloxacin).

\textbf{L-Ornithine—L-Aspartate}

\textit{L}-ornithine—\textit{L}-aspartate (LOLA) is a compound salt that stimulates ornithine transcarbamolylase and carbamoyl phosphate synthetase and is a substrate for the formation of urea. Also, LOLA works by stimulating glutamine synthesis in the skeletal muscle and, consequently, lowering ammonia. \textit{L}-ornithine—\textit{L}-aspartate has been most thoroughly evaluated in the setting of chronic HE. Two randomized, placebo-controlled, double-blind studies were performed in Germany using intravenous and oral forms of LOLA in patients with chronic HE, both of which found improvements in the number connection tests, ammonia values, and HE parameters (mental state gradation and Portosystemic Encephalopathy Index).\textsuperscript{32,33} Episodic, recurrent HE was specifically excluded from these studies. Few data exist for the management or prophylaxis of episodic OHE. One study from Pakistan evaluated LOLA as adjunctive treatment vs placebo in patients who were allowed to receive standard medical treatment (SMT).\textsuperscript{34} Patients with grade 2 HE or above had improvement in HE grade on SMT + LOLA (79\%) vs SMT + placebo (55\%), which was significant (\textit{P}=.019). In other countries, LOLA is used as adjuvant therapy, but this medicine is not available in the United States.

\textbf{Branched-Chain Amino Acids}

The plasma amino acid profile in patients with cirrhosis is altered, with a decrease in BCAAs and an increase in aromatic amino acids. The BCAAs are a source of glutamate, which helps to metabolize ammonia in skeletal muscle. The benefits of BCAAs in liver disease have been investigated for several decades. Supplementation with BCAAs may improve albumin synthesis, decrease insulin resistance, decrease hepatocellular carcinoma, and improve immune function.\textsuperscript{35} Two RCTs found that BCAAs improved important composite end points of death/hospitalization metrics in one study and hepatic failure, variceal bleeding, hepatocellular carcinoma, and mortality in a second study.\textsuperscript{36,37} Branched-chain amino acids have been studied in HE as well, to a lesser degree. An early study indicated that BCAAs were effective for latent (minimal) HE.\textsuperscript{38} More recently, BCAAs were administered to 58 patients with 1 previous episode of OHE and compared with 58 patients receiving maltodextrin.\textsuperscript{39} There was no significant difference in the frequency of recurrent HE. However, there was substantial loss to follow-up in this trial, so results must be interpreted cautiously. Currently, the European Society for Clinical Nutrition and Metabolism recommends the use of 1.2 g/kg per day of protein for compensated cirrhosis and 1.5 g/kg per day for decompensated cirrhosis. This recommendation was based on the results of an RCT of a normal protein diet (1.2 g/kg per day) vs a restricted diet reporting no effect on the outcome of episodic HE but increased muscle breakdown in the low-protein-diet group.\textsuperscript{40} In addition, the European Society for Clinical Nutrition and Metabolism provides a grade A recommendation for the use of standard protein supplementation in patients with HE grade 2 or less and BCAA preparations for HE grades 3 and 4.\textsuperscript{41}

\textbf{Percutaneous Embolization of Large Portosystemic Shunts}

Two large retrospective series have been published reporting the efficacy and safety of
embolization of large portosystemic shunts in medically refractory HE. In a European multicenter cohort study (n=37), 59% of patients were free of HE within 100 days and 48% were HE free an average of 2 years after embolization.42 There was 1 hepatic capsular hemorrhage, otherwise there were no other major periprocedural complications. Long-term safety seemed good, with no increase in variceal bleeding events. In the largest US series (n=15), 90% of patients with cirrhosis improved 2 months after the procedure.43 One patient developed an infected hepatic cyst 2 weeks after the procedure, otherwise there were no significant complications attributed to the procedure. The median MELD score in both studies was 13. Logistic regression performed in the European study suggested that patients with MELD score greater than 11 were at risk for HE recurrence after shunt embolization.

### Molecular Adsorbent Recirculating System

Molecular Adsorbent Recirculating System (MARS) was introduced in 1999 and is based on the concept of albumin dialysis. This system was designed to remove protein- and albumin-bound toxins, such as bilirubin, bile acids, nitrous oxide, and endogenous benzodiazepines (among others), and it also removes non–protein-bound ammonia that accumulates in liver failure. More than 45,000 MARS treatments have been administered to approximately 15,000 patients. Although the effect of MARS on survival for patients with liver failure remains in question, 3 studies44-46 have reported improvements in HE. The most recent and the largest trial (RELIEF Trial) enrolled 189 patients with acute-on-chronic liver failure and evaluated MARS plus SMT vs SMT alone on the primary end points of 28- and 90-day liver transplantation–free survival.45 Survival end points were not met, but safety was demonstrated. There was a higher proportion of patients with MELD scores greater than 20 (78.9% vs 69.7%, P=.16) and spontaneous bacterial peritonitis (14.4% vs 6.7%, P=.94) at baseline in the MARS treatment group. The proportion of patients with HE grade 3 or 4 improvement to HE grade 0 or 1 was higher in MARS-treated patients (15 of 24; 62.5%) compared with SMT (13 of 34; 38.2%), which trended toward significance (P=.07).45 In another study designed specifically to evaluate the effect of MARS on HE, 70 patients with grade 3 (56%) and grade 4 (44%) HE were randomized to receive MARS + SMT vs SMT alone.45 The primary end point was met whereby a higher proportion of patients had a 2-grade improvement in HE in the MARS arm (mean, 34%) vs the SMT arm (19%), with a P=.044 and more rapid improvement (P=.045).45 The MARS was also well tolerated in this trial. In the smallest study, MARS had a statistically significant effect on improvement of HE in 9 patients with alcoholic hepatitis and HE (without SMT) and decreased circulating aromatic phenolic amino acids.46 The FDA has approved the use of MARS for HE related to decompensation of chronic liver disease. Exclusion criteria in the 2 largest trials included active hemorrhage, active infections, severe cardiopulmonary disease, renal replacement therapy, and hemodynamic instability, which will decrease the applicability of MARS. Also, MARS may reduce the bioavailability of certain antibiotics.47 Cost is also a major concern with this modality. Nevertheless, MARS seems to be a viable option for patients with severe HE unresponsive to SMT.

### Evidence for Secondary Prophylactic/Maintenance Strategies for HE

#### Lactulose

The results of 2 recent trials provided solid evidence for the practice of secondary prevention with lactulose alone or lactulose and rifaximin. Sharma et al48 performed an open-label study randomizing 140 patients to receive placebo or daily lactulose after recovery from an episode of OHE. After dropouts and protocol violations, 19.7% of lactulose-treated patients (12 of 61) experienced recurrent OHE vs 46.9% (30 of 64) in the placebo arm (P=.001) over median follow-up of 14 months. In a similarly designed trial by Agrawal et al,49 patients recovered from OHE received lactulose (n=80), probiotics (n=77), or no therapy (n=78). Patients in the probiotic arm received 3 capsules per day containing 112.5 billion viable lyophilized bacteria per capsule containing 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium*, and 1 strain of *Streptococcus salivarius* subspecies thermophilus. The intention-to-treat results demonstrated a significantly lower rate of OHE for lactulose (37.5%) and probiotics (45.4%) compared with no treatment (64.1%). Ideally, these results should be reproduced in studies in other
countries/centers. The role of probiotics as stand-alone maintenance treatment is also interesting and deserving of further investigation.

**Rifaximin**

In 2010, Bass et al\(^{50}\) published results from an RCT of rifaximin (n=140) vs placebo (n=159) for the secondary prevention of episodic OHE in adult patients with 2 or more previous episodes of unprecipitated HE who were in remission at the time of enrollment. The MELD score was required to be 25 or less for participants. More than 90% of patients in both arms were taking lactulose. Patients experienced a reduction in breakthrough HE in the rifaximin group (31 of 140) compared with the placebo group (73 of 159), with a hazard ratio of 0.42 (95% CI, 0.28-0.64; \(P<.001\)). The authors also reported a 50% reduction in hospitalizations for the rifaximin group (19 of 140) compared with the placebo group (36 of 159). Adverse events were similar between the rifaximin and placebo groups. Based on data from this phase 3 study, rifaximin was approved by the FDA for the secondary prevention of OHE. It is important to reiterate that this trial did not address rifaximin use for episodic HE. A trial to evaluate the safety and efficacy of rifaximin in patients with cirrhosis with MELD scores of 25 or greater is under way (ClinicalTrials.gov Identifier: NCT01846663). Another ongoing trial is examining rifaximin plus lactulose vs rifaximin alone for secondary prevention (ClinicalTrials.gov Identifier: NCT01842581).

Patients with advanced MELD scores or Child-Turcotte-Pugh class B/C cirrhosis require secondary prophylaxis after recovery from spontaneous or precipitated episodic HE. Patients with Child-Turcotte-Pugh class A cirrhosis who are otherwise well compensated but develop isolated OHE in the setting of infection or gastrointestinal bleeding represent a more challenging decision. Some of these patients may not need or benefit from long-term maintenance treatment with lactulose, but data to drive patient selection for this strategy is not readily available. Decisions about secondary prophylaxis for these patients are made on a case-by-case basis, with no guidelines for best care. Ideally, these types of patients would receive neuropsychometric testing for CHE within a few weeks after leaving the hospital. However, neuropsychometric testing for CHE is not practical for most patients, and a simple clinical tool to detect CHE is badly needed. Patients with 1 previous precipitated (ie, gastrointestinal bleeding) OHE event, otherwise well compensated (Child-Turcotte-Pugh class A), and with lingering CHE as identified by specialized testing might warrant ongoing maintenance treatment with lactulose. However, this potential strategy requires further investigation before incorporating into standard clinical practice.

**APPROACH TO INDUCTION AND MAINTENANCE TREATMENT OF HE**

**Approach to Induction and Maintenance Treatment for the First Episode of Episodic OHE, West Haven Grades 1 and 2**

The first step in the management of episodic OHE is evaluation for the typical precipitants of OHE, including gastrointestinal bleeding, infections, new medications (such as opioids or benzodiazepines), constipation, diarrhea, dehydration, alkalosis or hypokalemia, and hypoxemia (Figure 1). Up to 80% of patients may have a precipitant. When a precipitant is found, management of the precipitant along with concomitant lactulose therapy is recommended. For those not responding to initial treatment, it is important to reevaluate the diagnosis of OHE, review the possibility of other precipitants, and ensure that the patient is having 3 to 4 stools per day while taking lactulose. For example, a head computed tomographic (CT) scan may be necessary in a patient who has a new focal neurologic defect on reexamination. If the diagnosis of OHE is correct, no other precipitants are found, and bowel movements are adequate, then neomycin or rifaximin could be added to lactulose therapy. Neomycin is FDA approved for this indication, but there are obvious concerns regarding nephrotoxicity, ototoxicity, and, to some degree, efficacy. Rifaximin use in this setting is off label. However, with the recent RCT reporting improved HE outcomes and a mortality benefit in patients taking lactulose with rifaximin, we recommend using rifaximin preferentially. Patients who recover from a first episode of OHE generally require lactulose maintenance therapy, especially if Child-Turcotte-Pugh class B/C.

**Approach to Induction and Maintenance Treatment for Recurrent (≥2 Episodes) Episodic OHE**

The management of recurrent OHE requires a careful evaluation for precipitating factors.
In addition, one must scrutinize the baseline maintenance medication regimen for these individuals. Inappropriate lactulose dose titration to achieve 3 stools per day and noncompliance are common. Patient education or reeducation is an important part of the management of this scenario. If symptoms such as bloating and excessive diarrhea occur, even while taking small doses of lactulose, rifaximin or neomycin should be substituted for lactulose. Breakthrough OHE while receiving an appropriate lactulose regimen calls for the addition of rifaximin (off label) or neomycin, although rifaximin is preferred. In more challenging patients who develop recurrent episodic OHE while appropriately using lactulose and rifaximin, the provider should consider looking for a large intra-abdominal portosystemic shunt with contrast-enhanced CT. In the trial of secondary prevention with lactulose by Sharma et al, the frequency of large spontaneous shunts was 23% (32 of 140) but may be present in up to 70% of patients with persistent HE. The risk of CT contrast nephropathy needs to be considered in these patients, who often have falsely normal creatinine levels with tenuous renal function; magnetic resonance angiography is an alternative for patients with a glomerular filtration rate greater than 30 mL/min per body surface area. For well-compensated patients with Child-Turcotte-Pugh class A cirrhosis or low MELD scores (arbitrarily defined as <12-15), percutaneous shunt embolization should be considered, which can result in remission from recurrent OHE in 59% to 90% of patients. Recurrent
OHE after shunt embolization is more likely with MELD scores greater than 11. If a shunt is not found or a high MELD score precludes embolization, then additional treatments, such as zinc, LOLA (where available), and BCAA feeding, should be considered. It is reasonable to check zinc levels in patients with HE to help guide dosing, using a 220-mg dose of zinc sulfate (contains 50 mg of elemental zinc) once daily in those with normal zinc levels. Once resolution of episodic OHE is achieved, all patients with recurrent OHE need to be maintained on lactulose, rifaximin, or both, depending on their initial therapy. For example, a patient with breakthrough OHE while taking lactulose will need a maintenance regimen of lactulose and rifaximin.

**Management of Severe HE (West Haven Criteria Grade 3 or 4)**

Grade 3 or 4 HE is a serious condition that requires intensive care unit monitoring (Figure 3). Patients who cannot protect their airway owing to decreased consciousness require endotracheal intubation and mechanical ventilation. After a thorough evaluation for precipitants, patients should be given lactulose via nasogastric (NG) tube. Lactulose at 15 to 30 cc can be given every 1 to 2 hours via NG tube until 3 stools are achieved. If NG or orogastric access is not available, then 300 cc of lactulose can be given in 1 L of water as an enema (300 cc of lactulose [10 g/15 mL] in 700 cc of sterile water). This can be repeated as necessary, although care should be taken to avoid excessively loose or voluminous stools.

---

**FIGURE 2.** Management of recurrent episodes of hepatic encephalopathy (HE), grade 1 or 2. *Rifaximin is not Food and Drug Administration approved for overt HE (OHE). abx = antibiotic; BCAA = branched-chain amino acid; LOLA = L-ornithine-L-aspartate; MELD = Model for End-Stage Liver Disease; PS = portosystemic.*

---

stool. We recommend down-titration or temporary interruption of lactulose administration in that circumstance. Rifaximin should be administered with lactulose in patients with grade 3 or 4 HE. Those who are diagnosed as having OHE, in whom precipitating factors have been sought and addressed, and who do not respond to lactulose and nonabsorbable antibiotics should be reevaluated to make sure that the diagnosis is accurate. If the diagnosis is in question, a head CT scan and an EEG may be helpful to rule out the possibility of a central nervous system bleeding event or nonconvulsive status epilepticus, respectively. If the diagnosis of OHE is accurate, then the patients should be evaluated for a large portosystemic shunt. A large shunt should be treated in the presence of refractory HE and relatively low MELD scores (<12-15). Most initial medication nonresponders will not have a large shunt and can be treated with BCAAs, zinc, and, where available, LOLA. Last, for patients not responsive to the aforementioned approach, MARS should be considered. Patients recovering from severe HE should be kept on a maintenance program of lactulose and rifaximin.

**DRIVING INSTRUCTIONS FOR PATIENTS LEAVING THE HOSPITAL**

Minimal HE is a risk factor for motor vehicle accidents (MVAs). Although the term CHE (which encompasses MHE) has replaced the term MHE, we will use the term MHE in this section as this
was the terminology used in the cited literature. It is likely that a substantial percentage of patients hospitalized for an episode of HE and who recover will have residual minimal encephalopathy after dismissal.\textsuperscript{52,53} Therefore, counseling at dismissal about the risks of driving is important. Some literature has amassed to quantify the magnitude of risk for MVAs in patients with MHE. Bajaj et al\textsuperscript{54} evaluated 167 cirrhotic patients prospectively for 1 year and identified 18 MVAs through Department of Transportation records. Of those 18 MVAs, 16 (89\%) occurred in patients identified as having MHE by the Inhibitory Control Test compared with 8 of 18 (44\%) by standard psychometric tests. Conversely, it is important to point out that approximately 55\% of patients who did not have an MVA were identified as having MHE. Another study assessed real-world driving ability in controls (n = 48), patients with cirrhosis without encephalopathy (n = 10), patients with MHE (n = 27), and patients with overt grade 1 HE (n = 14). Fitness to drive, as deemed by a driving instructor, was 87\% (control), 75\% (no HE), 48\% (MHE), and 39\% (grade 1 HE).\textsuperscript{55} An earlier on-road driving study found a substantial reduction in car handling, adaptation, and cautiousness in patients with MHE (n = 14) compared with controls or cirrhotic patients without MHE.\textsuperscript{36} The instructor had to intervene on 5 of 14 patients with MHE to avert an accident. In summary, some patients with MHE have impaired driving skills, which can translate into real-world risk of MVAs. Yet, we do not have widely available and practical tools to predict who is at risk.

What are the medicolegal ramifications for the provider? No states have specific legislation that pertains to patients with HE. Only 6 states have mandatory reporting laws requiring the physician to report drivers with general medical impairment: California, Delaware, Nevada, New Jersey, Oregon, and Pennsylvania. Of the remaining 44 states, 25 provide legal immunity to physicians for reporting patients who have medical impairments.\textsuperscript{57}

We recommend that treating physicians consider testing for MHE if they are in tertiary care centers with access to these tests. Patients found to have MHE should return to their licensing agency for a road test. It has been suggested, based on positive driving simulator evidence, that patients who have MHE and have failed a driving test could be treated with rifaximin and repeat the driving test.\textsuperscript{36} However, this strategy cannot be endorsed for all patients at this time without more evidence. In a cost-effectiveness analysis, using the Inhibitory Control Test to diagnose MHE and treatment with lactulose to prevent MVAs would be cost saving. Treatment with rifaximin would save costs in this context only if the monthly cost was less than $353.\textsuperscript{59}

CONCLUSION
In summary, HE eventually occurs in up to 50\% of cirrhotic patients and heralds a poor prognosis. Patients with episodic OHE are primarily cared for in the hospital. Treatment of the hospitalized patient with episodic OHE can be compartmentalized into induction treatment and maintenance of remission. Lactulose remains the cornerstone of treatment for induction and maintenance of remission. There is now evidence to support the use of rifaximin as adjunctive therapy for severe OHE, but it is not yet FDA approved for this indication. Alternatively, neomycin can be used as adjunctive therapy, but its adverse side effect profile makes it a less attractive choice. Percutaneous embolization of large portosystemic shunts and MARS therapy are emerging modalities with evidence to support their use for medically refractory OHE. Most patients require maintenance medications when dismissed from the hospital, and patient/caregiver education about the role of those medications and appropriate dose titration for lactulose is crucial. Rifaximin should be added to lactulose treatment for patients with recurrent OHE. All patients and their families should be counseled about the risks of MVAs. Mandatory state reporting laws should be followed. It is recommended that these patients have a fitness-to-drive evaluation in the outpatient setting.

**Abbreviations and Acronyms:** abx = antibiotic; BCAA = branched-chain amino acids; CHE = covert hepatic encephalopathy; CT = computed tomography; dx = diagnostic; EEG = electroencephalogram; FDA = Food and Drug Administration; HE = hepatic encephalopathy; LOLA = l-ornithine–l-aspartate; MARS = Molecular Adsorbent Recirculating System; MELD = Model for End-Stage Liver Disease; MHE = minimal hepatic encephalopathy; MVA = motor vehicle accident; NG = nasogastric; OHE = overt hepatic encephalopathy; RCT = randomized controlled trial; SMT = standard medical treatment

**Potential Competing Interests:** Dr Kim served as an advisory board member for Salix Pharmaceuticals Inc, Raleigh,
REFERENCES


**MANAGEMENT OF HEPATIC ENCEPHALOPATHY**


www.mayoclinicproceedings.org