

Overt Hepatic Encephalopathy: Pharmacotherapy Review

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INTRODUCTION

Hepatic encephalopathy (HE) has a large impact on the patient, caregivers, and health care team. From 2005 to 2009, there were 110,000 hospitalized patients in the United States.¹ Overt hepatic encephalopathy (OHE) may occur in up to 50% of all cirrhotic patients.² In 2013, the American Association for the Study of Liver Diseases (AASLD) in conjunction with the European Association for the Study of the Liver (EASL) released a treatment guideline for the management of hepatic encephalopathy. In addition to developing the definition and classification, treatment approaches were developed with a caveat that the evidence supporting treatment was not the most robust.¹ This review is of the recommendations from the guidelines, as well as a review of specific literature.

AASLD/EASL hepatic encephalopathy utilized the following score for determining the level of evidence behind each recommendation (table 1).

Table 1. GRADE system for evidence

Grade	Evidence
I	Randomized, control trials
II-1	Controlled trials, without randomization
II-2	Cohort or case-control studies
II-3	Multiple time series, uncontrolled experiments
III	Expert opinion or descriptive epidemiology
Evidence	Description
High quality	Further evidence unlikely to change the estimated effect

A

Moderate	Further research is likely to have important impact on our confidence in the estimation of effect and may change the estimate	B
Low quality	Further research is likely to have important impact on our confidence in the estimation of effect and is likely to change the estimate	C
Recommendation		
Strong	Factors influencing the quality of the recommendation include quality evidence, patient important factors, and costs	1
Weak	More uncertainty, variance in preference or values. Recommendation with less certainty, higher costs, or resource consumption.	2

HE has been defined as the brain dysfunction in patients with liver failure with or without portosystemic shunting that results in neurological or psychological abnormalities.² Initiation of therapy for the treatment of HE should begin, but identifying and treating the underlying precipitating factor is paramount to successful treatment. Therapies for treatment of hepatic encephalopathy include nonabsorbable disaccharides (lactulose), rifaxamin, and other treatments.¹

Nonabsorbable Disaccharides

AASLD recommends that the first line of therapy is lactulose (GRADE II-1, B, 1) and lactulose use for prevention of recurrent episodes (GRADE II-1, A, 1).¹ Lactulose produces reduction of ammonia levels through acidification of the colon which results in conversion of ammonia to ammonium which elicits a prebiotic effect. In addition lactulose, lactitol, and polyethylene glycol (PEG) produce a cathartic effect. While the evidence supporting the use of lactulose is limited by the methodological deficiencies, the decades of use and cost comparison have led to continued recommendation of use.

Lactulose vs. PEG-3350

A recent article published in JAMA by Rahimi et al studied the use of PEG-3350 solution versus lactulose in hepatic encephalopathy. It was hypothesized that catharsis of the gut would lead to relief in OHE, which would make PEG-3350 superior to lactulose. Primary endpoint was decrease in hepatic encephalopathy scoring algorithm (HESA) score from baseline (table 2).

Table 2. HESA Scoring System

Criteria for Scoring	
Grade 4	Must include each of the following: <ul style="list-style-type: none"> • No eyes opening • No reaction to simple commands • No verbal response

Grade 3 3 or more of the following:

- Somnolence
- Confusion
- Disorientated to place
- Bizarre behavior/anger/rage
- Clonus/rigidity/nystagmus/Babinsky
- No mental control*

Grade 2 Any 3 of the following:

- Lethargy
- Hyperactive reflexes
- Loss of time
- Inappropriate behavior
- Slurred speech

Or any 2 of the following:

- Slow responses*
- Anxiety*
- Amnesia*
- Impaired simple computation*

Grade 1 Any 4 of the following:

- Sleep disorder/impaired sleep
- Tremor
- Impaired complex computations*
- Short attention span*
- Impaired construction ability*
- Euphoria or depression*

Grade 0 Does not meet any other grade criteria

*Symptoms assessed using neuropsychological measures

The study observed the use of either lactulose or PEG-3350 4-Liters in 50 patients. The authors found that PEG-3350 was superior to reducing HESA scores over 24 hours. In the lactulose arm, 52% of patients reached the primary endpoint compared to 91% of patients in the PEG-3350 group ($p < 0.01$). Additionally, the mean (\pm SD) HESA score change was greater with PEG-3350 treatment (1.5 ± 0.8) versus lactulose (1.5 ± 0.8) ($p < 0.002$), and median time to resolution of HE was shorter with PEG-3350 ($p = 0.01$). Side-effects were comparable between groups with diarrhea being more prevalent in the PEG-3350 arm and bloating being more common in lactulose. Electrolyte abnormalities and dehydration were not significantly different between treatment arms, although the study may have been underpowered to detect this.

There were many limitations to this study. First, there was limited blinding as it was impossible to blind the PEG-3350 container. Additionally, it was a small, single-centered study. Even though the study technically met power, the effect to lactulose may have been underestimated and a large effect size for PEG-3350 was assumed. Regardless of these limitations, a large effect was observed and PEG-3350 is as widely available and affordable as lactulose. Further studies on the use of PEG-3350 for HE may be warranted.³

Rifaximin

The intestinal production of ammonia and its absorption is reduced due to the alteration in the gastrointestinal microflora from the administration of rifaximin. An additional benefit is the lack of systemic side effects seen as rifaximin is not absorbed. The AASLD guidelines recommend

rifaximin as an effective additional therapy for patient on lactulose to prevent the recurrence of episodes (GRADE I, A, 1).¹

Lactulose vs. Rifaximin

The controversy of using rifaximin either in place of or in addition to lactulose has waged on despite current practice guidelines that recommend lactulose as first-line treatment. Rifaximin proved effective compared to placebo in 299 patients with recurrent encephalopathy (HE) who were in remission. Rifaximin 550 mg twice daily did reduce the risk of an episode of hepatic encephalopathy (HR 0.42; 95% CI [0.250-0.64]) as well as the risk of hospitalization from hepatic encephalopathy (HR 0.50; 95% CI [0.29 – 0.87]). Of note, over 90% of patients in each arm were on baseline lactulose and upon sub-group analysis, those patients who were not using lactulose at baseline had no significant differences in outcomes with rifaximin compared to placebo. Overall, treatment was well tolerated and rifaximin had positive outcomes.⁴

In one study by Leevy and Phillips, investigators sought to compare frequency and duration of hospitalizations related to hepatic encephalopathy with rifaximin versus lactulose. Charts of 145 patients using lactulose 30mLs twice daily for ≥ 6 months or rifaximin 400mg three times daily for ≥ 6 months were retrospectively reviewed. Less patients taking rifaximin were hospitalized during the treatment period versus those taking lactulose, had shorter hospitalization time, and lower hospitalization charges ($p < 0.001$ for all measures). Diarrhea, flatulence, and abdominal pain were reported more in the lactulose group over rifaximin ($p < 0.001$). Of note, a low compliance rate (defined as missing $< 25\%$ of doses) was noted in a large percentage of lactulose patients (31%) versus rifaximin patients (92%) and was attributed to poor tolerability. Another limitation would be the dosing strategies used. Many patients may require higher doses of lactulose (titrated to 3 to 4 loose stools per day) than twice daily. Additionally, recommended dosing for rifaximin in hepatic encephalopathy ranges and is often 550mg twice daily instead of 400mg three times daily.⁵

Probably the most common prescribing method is the use of rifaximin with lactulose. A study by Sharma et al demonstrated this by comparing lactulose alone to lactulose plus rifaximin. This study evaluated 120 patients with overt HE ($>80\%$ grade 3 or 4) who were randomized to receive either lactulose alone or lactulose plus rifaximin. Baseline Child-Pugh was mainly Class B and C and Mean MELD was 24.5 ± 4.2 . Of these patients, 55 had experienced previous episodes of HE requiring treatment, but no patients were refractory to treatments. There were more patients in the combination therapy group that experienced reversal of HE symptoms within a 10 day period (76% vs. 44% lactulose alone; $p = 0.004$). Patients treated with both lactulose and rifaximin also experience shorter hospital stays ($p = 0.01$) and a decrease in mortality ($p < 0.05$; ARR 25.1%) with a number needed to treat of 4. There were no notable differences in patients who died due to gastrointestinal bleed or hepatorenal syndrome, but there were more deaths due to sepsis in patients treated with lactulose alone. There were no serious side effects related to either treatment arm reported with respect to abdominal pain or diarrhea. The authors hypothesized the different mechanisms of action on gut flora resulted in synergistic action and increased efficacy of the two treatments together.⁶

Other studies have shown rifaximin is as effective and possibly superior than conventional therapies such as lactulose and is well tolerated. However, there is still a lack of evidence to support rifaximin as sole therapy for HE and the cost of rifaximin greatly exceeds the cost of lactulose. With the available data and the updated guidelines from the AASLD, the recommendation is still lactulose as first choice for the treatment of HE or for prevention of recurrent HE episodes after initial episode and rifaximin as effective add-on therapy.^{1,7,8}

Other therapies

The guidelines currently address other therapies available for use including branch-chained amino acids (BCAAs), L-ornithine L-aspartate (LOLA), Probiotics, Glutaminase inhibitors, neomycin, metronidazole, albumin, or laxatives. The guidelines conclude BCAA's, LOLA, neomycin, and metronidazole may have a role for refractory patients who fail to respond to conventional therapy. Other therapies lack evidence that show benefit and should not be recommended at this time. (AASLD)

Summary and Recommendations

Overt hepatic encephalopathy remains a significant complication of cirrhosis. The updated AASLD guidelines highlight the need for better controlled clinical treatments for effects of different forms of HE and specific complications. There is also a lack of standardization between trials which makes comparing treatments difficult. Future studies need to better assess effects of HE on individual and societal costs, diagnostic tools, and therapeutic goals.

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