

# Pharmacologic Management of Hepatic Encephalopathy



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## KEYWORDS

• Hepatic encephalopathy • Nonabsorbable disaccharides • Lactulose • Rifaximin

## KEY POINTS

- Hepatic encephalopathy pharmacologic management.
- Mechanism of therapies for hepatic encephalopathy.
- Hepatic encephalopathy first-line therapies.
- Hepatic encephalopathy second-line therapies.

## INTRODUCTION

Medical management of the patient with hepatic encephalopathy first relies on several key principles of appropriate supportive care. This includes appropriate triage of patients based on the grade of hepatic encephalopathy to outpatient therapy, inpatient therapy, or intensive care unit (ICU) for closer monitoring and airway management. Additionally, reversal of common precipitants such as bleeding, infection, volume depletion, and renal failure is vital to ensuring increased efficacy of any of the below treatments. The first step for any patient with hepatic encephalopathy is to tailor management according to the ABCs of hepatic encephalopathy (ie, acute liver failure or portosystemic shunting or acute on chronic liver failure and cirrhosis). However, in terms of pharmacologic therapy, patients with overt hepatic encephalopathy have been shown to benefit from a rather restrictive number of pharmacologic therapies.

## ELECTROLYTE DISTURBANCES, HYPOKALEMIA

Management of hypokalemia is essential for successful treatment of hepatic encephalopathy. It has been long hypothesized that potassium depletion increases serum ammonia and therefore the risk of overt hepatic encephalopathy. In 1962, Baertl and colleagues demonstrated that a diuretic regimen in patients with cirrhosis led to an increase in serum ammonia, with subsequent development of hepatic encephalopathy. Other studies from the 1950s and 1960s demonstrated similar results.<sup>1</sup> The

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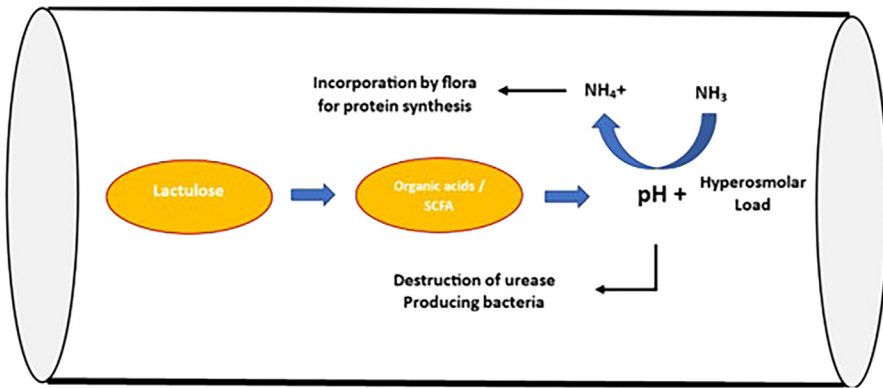
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proposed mechanism behind this association is renal metabolism of glutamine to enable recovery of potassium within the proximal tubule, a process that produces ammonium as a byproduct. In fact, studies have shown that hypokalemia is associated with longer ICU stays, higher mortality, and increased severity of hepatic encephalopathy.<sup>2</sup> Ullah and colleagues' cross-sectional study of 5000 patients with hepatic encephalopathy revealed a direct association with the degree of hypokalemia and the grading of hepatic encephalopathy, with 60% of patients with serum potassium less than 2.5 mEq/L being diagnosed with grade 4 hepatic encephalopathy, compared with 6.4% of patients with serum potassium greater than 3.4 mEq/L.<sup>3</sup> However, given the lack of available randomized controlled trial (RCT) evaluation of potassium supplementation and hepatic encephalopathy resolution, it remains unclear whether hypokalemia directly increases severity of hepatic encephalopathy, or that it is a prognostic marker for worsening decompensation. Regardless, given the available data supporting the physiologic mechanism linking hypokalemia to increased serum ammonia levels, it is reasonable to recommend potassium supplementation for correction of hypokalemia in hospitalized patients with overt hepatic encephalopathy.

### NONABSORBABLE DISACCHARIDES

In general, the mainstay of traditional pharmacologic therapy for hepatic encephalopathy is aimed at lowering serum ammonia concentration. Of the available treatments, nonabsorbable disaccharides such as lactulose (a disaccharide of fructose and galactose) and lactitol have remained the most easily accessible and commonly used treatment modalities. Lactulose is inexpensive, readily available across most institutions, associated with only mild gastrointestinal side effects and is available in both an oral and rectal formulation should the patient be unable to tolerate oral medications. Lactulose and lactitol exert their effect on serum ammonia via multiple proposed mechanisms. It is believed the primary mechanism is the reduction of stool pH by lactulose, which favors the conversion of ammonia to ammonium, trapping it in the colonic membrane and instead promoting its utilization of its nitrogen for protein synthesis by the colonic flora. This reduction in pH is also thought to favor the destruction of urease producing bacteria, further reducing ammonia production via changes in the microbiota. An additional potential mechanism includes the laxative effect produced by the metabolism of sugars by colonic bacteria, reducing transit time and thus ammonia absorption (Fig. 1).<sup>4</sup> A typical effective dose to achieve these effects is 20 to 30 mg of lactulose every 2 hours, titrated to achieve 2 to 3 soft stools per day.

In 1969 Elkington and colleagues' small RCT demonstrated such a reduction in stool pH and ammonia concentration as well as improvements in electroencephalogram readings among patients receiving lactulose therapy compared with those receiving sorbitol.<sup>5</sup> Since then, numerous other studies, including a 2016 Cochrane review of 38 RCTs of 1828 patients have demonstrated similar beneficial responses of lactulose compared with placebo (relative risk [RR], 0.58; 95% CI, 0.50–0.69) among most patients with overt hepatic encephalopathy.<sup>6</sup> A more recent 2020 systemic review and meta-analysis of 1563 patients, when comparing lactulose to placebo, showed improved reversal of minimal hepatic encephalopathy (odds ratio [OR], 5.39; 95% prediction interval [PrI], 3.6–8.0; surface under the cumulative ranking curve [SUCRA], 67.2%; moderate quality) as well as prevention of overt hepatic encephalopathy (OR, 0.22; 95% PrI, 0.09–0.52; SUCRA, 73.9%; moderate quality).<sup>7</sup> However, it is important to note that during the several decades since its widespread use, large, rigorous, well-designed RCTs are limited, and so the evidence for nonabsorbable disaccharides is derived mostly from such systematic reviews. Despite these limitations



**Fig. 1.** Proposed mechanism of lactulose. Breakdown of lactulose by colonic bacteria produce short-chain fatty acids and other organic acids, reducing stool pH. This reduction in stool pH converts ammonia to ammonium, trapping it inside the colonic lumen and making it available for incorporation by the colonic flora into proteins. Additional mechanisms include the destruction of urease-producing bacteria by the reduction in stool pH, as well as an increase in hyperosmolar load via the production of organic acids, which then leads to a laxative effect, eliminating ammonia from the body.

in the available literature, lactulose remains the preferred first-line therapy for hepatic encephalopathy, partly because of its low price and thus high cost-effectiveness.<sup>8</sup>

Furthermore, RCTs by Sharma and colleagues and Agrawal and colleagues have demonstrated similar beneficial effects in the secondary prophylaxis of hepatic encephalopathy. Sharma and colleagues demonstrated a reduction in subsequent episodes from 47% with placebo to 20% with lactulose.<sup>9,10</sup> For this reason, both the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend continued use of lactulose after an initial episode of overt hepatic encephalopathy for secondary prophylaxis. Dosing remains similar to what is given for the reversal of overt symptoms.

## POLYETHYLENE GLYCOL

If one of the mechanisms by which nonabsorbable disaccharides reduce serum ammonia is via a laxative effect, then it would be reasonable to hypothesize that other laxatives may be equally as efficacious. The 2014 HELP randomized clinical trial separated 50 patients with hepatic encephalopathy into either standard treatment with lactulose or treatment with 4 L of polyethylene glycol. Patients receiving polyethylene glycol saw resolution in hepatic encephalopathy at a median of 1 day, compared with 2 days for standard therapy with lactulose.<sup>11</sup> A 2021 systemic review and meta-analysis looked at studies similar to the HELP trial, for a total of 4 trials with 229 patients. The authors found that patients treated with polyethylene glycol scored lower on the hepatic encephalopathy scoring algorithm at 24 hours (mean difference,  $-0.68$ ; CI,  $-1.05$  to  $-0.31$ ) were more likely to have a score of 0 at 24 hours (RR,  $-4.33$ ; CI,  $2.27$ – $8.28$ ) and have an overall shorter time to resolution of hepatic encephalopathy (MD,  $-1.45$ ; CI,  $-1.72$  to  $-1.18$ ).<sup>12</sup> Despite the promising results so far for polyethylene glycol, evidence remains much sparser than that favoring treatment with lactulose. Additionally, the large volume required for treatment may not be effective in patients who are altered and may be higher aspiration risks. Whether there remains

a role for polyethylene glycol in patients either unable to tolerate lactulose or have enteral access allowing easier administration of the 4 L required remains to be seen.

## ANTIBIOTICS

Antibiotics to reduce serum ammonia concentrations have an established role in hepatic encephalopathy treatment. For many years neomycin, a glutaminase inhibitor, was the antibiotic of choice in reducing the burden of ammonia-producing bacteria. Early studies comparing neomycin and lactulose showed promising results, with several studies suggesting almost equal efficacy between the 2 treatments.<sup>13</sup> However, other subsequent studies were conflicting in their results. As an example, a randomized clinical trial of 102 cirrhotic patients with hepatic encephalopathy during hospital admission did not find a significant difference in resolution between patients receiving neomycin and those receiving placebo.<sup>14</sup> Additionally, neomycin has been repeatedly associated with significant adverse effects, including ototoxicity, nephrotoxicity, and neurotoxicity.<sup>15</sup> Evidence for other antibiotics, such as metronidazole, is even more lacking.

Several earlier studies have demonstrated promising results for rifaximin, a minimally absorbed oral antibiotic with both anaerobic and aerobic coverage of several gram positive and gram-negative bacteria. It is hypothesized that rifaximin works by altering the gut microbiota composition and enhancing the function of “positive microbiota” while also reducing the production of proinflammatory cytokines, although robust evidence for these hypotheses remains lacking.<sup>16</sup> A typical dose for rifaximin after an episode of hepatic encephalopathy is 550 mg twice daily for at least 3 months.

In 2003, an RCT of 103 patients by Mas and colleagues comparing lactulose with rifaximin demonstrated equal efficacy in the treatment of overt hepatic encephalopathy (81.6% vs 80.4%).<sup>17</sup> Since then, several more studies have demonstrated more promising results when comparing rifaximin against various other treatments for hepatic encephalopathy. In a subsequent 2013 RCT of 120 patients by Sharma and colleagues, the combination of lactulose and rifaximin proved superior to lactulose alone in the reversal of overt hepatic encephalopathy (76% vs 50.8%).<sup>8</sup> A 2014 systematic review by Kimer and colleagues demonstrated equal or greater efficacy for rifaximin with increased recovery from overt encephalopathy (RR, 0.59; CI, 0.46–0.76) and reduced mortality (RR, 0.68; CI, 0.48–0.97) when compared with lactulose, neomycin, and other antibiotics such as metronidazole. Overall, the number needed to treat was 4 when placebo controlled, 7 when lactulose controlled, and 6 when other antibiotics were used as the control.<sup>18</sup>

In terms of secondary prophylaxis, a 2010 RCT of 299 patients with a recent episode of hepatic encephalopathy found that rifaximin reduced the risk of a subsequent episode from 46% to 22% at 6 months,<sup>19</sup> with other studies demonstrating similar results. For this reason, most practitioners will use rifaximin in conjunction with lactulose for the prevention of overt hepatic encephalopathy in patients who have had a breakthrough episode while on lactulose. This practice is in line with both AASLD and EASL guidelines for the secondary prophylaxis of hepatic encephalopathy.

One of the drawbacks of rifaximin is its water-insolubility and dependence on bile acids for maximum effectiveness. In patients with liver disease microbiota dysbiosis resulting in bile acid imbalances may therefore reduce the effectiveness of rifaximin. More recently, a new soluble solid dispersion form of the medication has demonstrated increased water solubility with minimal system exposure and is available in both an immediate release and sustained release preparation. In a 2023 phase II clinical trial of 71 patients with overt hepatic encephalopathy, the immediate release

version of this new formulation, when added to lactulose, reduced the median time to resolution of hepatic encephalopathy from 62.7 hours to 21.1 hours, when compared with lactulose alone.<sup>20</sup>

For these reasons, rifaximin, now approved by the Food and Drug Administration for treatment of hepatic encephalopathy, has largely overtaken other antibiotics such as neomycin and metronidazole. However, given the lower cost and ease of access with lactulose, rifaximin is used primarily as an adjunct to lactulose. Although some studies suggest that given its lower side-effect profile, the increased rate of adherence to rifaximin compared with lactulose may prevent hospitalizations for hepatic encephalopathy and thus make it perhaps even more cost-effective than lactulose, the available evidence is not strong enough to suggest a transition to rifaximin as the first-line therapy.<sup>9</sup> However, in patients who cannot tolerate lactulose due to its gastrointestinal side effects, rifaximin monotherapy may be a reasonable choice.

## ALBUMIN

Albumin has seen widespread use among patients with decompensated cirrhosis, primarily for volume expansion and the treatment of hepatorenal syndrome. More recently, it has also been investigated as a potential pharmacologic therapy in the treatment of hepatic encephalopathy. Specifically, it is hypothesized that albumin infusions may reduce the level of proinflammatory cytokines as well as endothelial dysfunction, both of which may play a part in the precipitation of overt hepatic encephalopathy. This would allow for a therapeutic target separate from ammonia production and thus supplement the effect of the previously mentioned therapies.

A 2013 randomized control trial by Simon-Talero and colleagues assigned a total of 56 patients with grade II to IV hepatic encephalopathy to either receiving albumin with lactulose or saline with lactulose. Although there were no significant differences in hepatic encephalopathy at day 4, by day 90 there was a significant difference in survival favoring patients who received albumin (69.2% vs 40.0%). However, the authors admit that this difference in survival may have been that hepatic encephalopathy identifies more severely decompensated patients who may benefit from the anti-inflammatory properties of albumin.<sup>21</sup> A 2021 meta-analysis examined a total of 12 studies, with 2087 patients, and found that among patients with overt hepatic encephalopathy, albumin infusion resulted in a lower overall risk (OR, 0.43; CI, 0.27–0.68). Furthermore, they also found a lower risk of developing overt hepatic encephalopathy in patients without any overt symptoms at baseline (OR, 0.53; CI, 0.32–0.86).<sup>22</sup>

Most recently, a 2023 double-blind randomized placebo-controlled trial by Fagan and colleagues, the HEAL study, looked at the impact of albumin on the prevention of hepatic encephalopathy. A total of 48 patients with prior hepatic encephalopathy or minimal hepatic encephalopathy despite treatment with standard of care were either treated with 25% IV albumin 1.5 g/kg or saline for 5 weeks. At 1 week after the last infusion, patients who received albumin had improvements in minimal hepatic encephalopathy scores, increased quality of life, and decreased endothelial dysfunction and inflammation interleukin 1 beta (IL-1B).<sup>23</sup> Although more studies are needed, this study and previous meta-analyses seem to indicate that there may be a role for albumin administration in patients with residual cognitive dysfunction despite treatment with standard of care.

## BRANCHED-CHAIN AMINO ACIDS

It was previously thought that decreasing protein intake in patients with cirrhosis would decrease sources of nitrogen and thus serum ammonia levels and risk of overt

hepatic encephalopathy. This has since been proven to be false, and it is instead now suggested to maintain a protein intake of at least 1.2 to 1.5 g/kg/d given the level of sarcopenia evident in most patients with cirrhosis. However, there does seem to be a subset of patients in whom protein intake is related to increase in serum ammonia. Among these patients, substitution of fish, milk, and meat protein with vegetable protein is thought to ameliorate this increase. This is thought to be due to not just the amino acid composition of vegetable proteins themselves but also the presence of fiber, which contains some level of nonabsorbable disaccharides.<sup>24</sup>

Another alternative to fish, milk, and meat protein is the administration of branched-chain amino acids. A 2015 cochrane review examined a total of 16 RCTs with 827 patients with overt or minimal hepatic encephalopathy confirmed a beneficial effect on branched-chain amino acids on hepatic encephalopathy (RR, 0.73; CI, 0.61–0.88). However, analysis of trials that compared branched-chain amino acids to lactulose or neomycin rather than placebo or just diet found no benefit (RR, 0.66; CI, 0.34–1.30).<sup>25</sup> The overall available evidence of branched-chain amino acids remains weak, although there does seem to be some role for supplementation in patients who are unable to tolerate protein intake or have no enteral access for nutritional support.

## PROBIOTICS

The use of prebiotics such as nonabsorbable disaccharides may exert some of their clinical benefit via alterations in the gut microbiome. Therefore, it would not be unreasonable to assume that probiotic therapy may also play a role in the treatment of hepatic encephalopathy. A small 2008 randomized trial of 25 patients receiving a probiotic yogurt demonstrated significant reversal in minimal hepatic encephalopathy (71% vs 0%) and a reduction in the development of overt hepatic encephalopathy (0% vs 25%).<sup>26</sup> A 2017 meta-analysis of 21 trials with 1420 patients looked at the effectiveness of probiotics when compared with either placebo or lactulose. When compared with placebo, there was no effect on mortality but there was a lower rate of “no-recovery” (RR, 0.67; confidence interval [CI], 0.56–0.79) and a decrease in plasma ammonia (MD,  $-8.29 \mu\text{mol/L}$ ; CI,  $-13.17$  to  $-3.41$ ). However, when compared with lactulose, these beneficial effects disappeared.<sup>27</sup>

A 2014 RCT of 160 patients by Lunia and colleagues looking specifically at the prevention of hepatic encephalopathy found that patients receiving probiotics, when compared with placebo, were less likely to develop overt HE (hazard ratio [HR], 2.1; CI, 1.31–6.53) and were also noted to have reduced levels of arterial ammonia.<sup>28</sup> Other studies looking at secondary prophylaxis have found similar results, although when compared with lactulose the benefit does not seem to be statistically significant.<sup>10</sup> Despite the significant limitations in studies looking at probiotics, especially since any systemic review or meta-analysis is likely to combine various forms of probiotics, there is promising data at least for the prevention of overt hepatic encephalopathy, if not for its treatment. More data are needed on the impact of specific microbes on overall ammonia balance before more promising trials can be conducted.

The current available data for the use of fecal microbiota transplant as a potential therapy for hepatic encephalopathy are even more limited than that of probiotics. A small 2017 open-label RCT of 28 patients with recurrent hepatic encephalopathy compared standard of care with pretreatment with broad-spectrum antibiotics followed by fecal microbiota transplant from a single donor with an “optimal” microbiota found some benefit. The authors found decreased incidence of further hepatic encephalopathy, improved cognition, and increased diversity and beneficial taxa.<sup>29</sup>

Just as with probiotics, more data are needed before fecal microbiota transplants can be recommended as a potential therapy for even refractory recurrent hepatic encephalopathy.

### **Zinc**

Zinc is an essential trace element vital for the activity of urea cycle enzymes as well as glutamine synthetase in muscle cells. For this reason, zinc deficiency, noted to be common among patients with cirrhosis, has been postulated to be directly linked to an increase in serum ammonia levels.<sup>30</sup> However, although this mechanistic link seems clear, the data for zinc supplementation to treat or prevent hepatic encephalopathy remain less clear. Older studies demonstrating conflicting results for the benefit of zinc supplementation have more recently been criticized because many of these studies also involved protein restriction, which as noted above is now thought to be detrimental in the prevention of hepatic encephalopathy, and newer studies are sparse. Takuma and colleagues' 2010 study of 79 patients with cirrhosis and hepatic encephalopathy randomized patients to either zinc in addition to standard therapy, defined as protein-restriction with branched-chain amino acids and lactulose, or standard therapy alone. They found that in multivariate analysis, zinc supplementation improved physical component scales but not mental component scales.<sup>31</sup> A systematic review of 4 trials with 233 patients, including the previously mentioned trial by Takuma and colleagues, found that zinc supplementation was not associated with encephalopathy recurrence, mortality, liver-related morbidity, or quality of life.<sup>32</sup>

### **L-Ornithine-L-Aspartate**

L-ornithine-L-aspartate (LOLA) is thought to lower serum ammonia levels via the activation of carbamyl phosphate synthetase, which converts ammonia to urea, as well as glutamine synthetase, which metabolizes ammonia to glutamine. A 2015 systemic review of 28 RCTs looking available therapies for hepatic encephalopathy, LOLA improved clinical efficacy when compared with no intervention more so than any other intervention (OR, 3.71; CI, 1.98–6.98). However, no statistically significant difference was seen when comparing LOLA directly to other standard therapies including lactulose and rifaximin.<sup>33</sup> A 2019 meta-analysis of 10 RCTs with 919 patients showed a benefit for both low-grade and high-grade hepatic encephalopathies, including improvement in metal state grade by West Haven, psychometric testing, and fasting blood ammonia. When compared with lactulose, rifaximin, probiotics, and branched-chain amino acids, LOLA was found to be equally efficacious, with a possible trend toward superiority.<sup>34</sup> More recently, a 2020 phase 2b trial of a related ammonia scavenger, ornithine phenylacetate, found no difference in median time to improvement when compared with placebo.<sup>35</sup> However, well-designed, large RCTs remain lacking, and despite being used in other countries, LOLA remains inaccessible in the United States.

### **CLINICS CARE POINTS**

- Patients with overt hepatic encephalopathy have been shown to benefit from a restrictive number of pharmacologic therapies. The most commonly used and evidence-based therapies include nonabsorbable disaccharides (e.g. lactulose) and the minimally absorbed oral antibiotic rifaximin.
- The 2014 HELP trial demonstrated promising results for the use of polyethylene glycol in hepatic encephalopathy. Similarly, the 2023 HEAL study demonstrated promising results

for the use of albumin. Both of these medications are readily available across healthcare facilities, however more robust data is needed before their use can be recommended as a first line agent alongside lactulose and rifaximin.

- Studies on branched-chain amino acids, probiotics, zinc supplementation, and L-ornithine-L-aspartate (LOLA) have all demonstrated mixed results, and so their use for the treatment of hepatic encephalopathy must be considered on a case-by-case basis.

## DISCLOSURE

No disclosures related to the article.

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