



Review Article

Novel Agents in the Management of Hepatic Encephalopathy: A Review

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Abstract

Hepatic encephalopathy is an often devastating complication of chronic liver disease, associated with high mortality and increased burden on patients and healthcare systems. Current agents (such as nonabsorbable disaccharides and oral antibiotics) are often only partially effective and associated with unpleasant side effects. With our improved understanding of the pathophysiology of hepatic encephalopathy, multiple treatment modalities have emerged with promising results when used alone or as an adjunct to standard medications. The mechanisms of these agents vary greatly, and include the manipulation of gut microbial composition, reduction of oxidative stress, inhibition of inflammatory mediators, protection of endothelial integrity, modulation of neurotransmitter release and function, and other novel methods to reduce blood ammonia and neurotoxins. Despite their promising results, the studies assessing these treatment modalities are often limited by study design, sample size, outcome assessment heterogeneity, and paucity of data regarding their safety profiles. In this article, we discuss these novel agents in depth and provide the best evidence supporting their use, along with a critical look at their limitations and future directions.

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Introduction

Hepatic encephalopathy (HE) is a serious and common com-

plication of liver dysfunction, encompassing a broad spectrum of neurocognitive and psychomotor dysfunction ranging from disorientation to coma.¹ It is classified into three major subtypes, based on the underlying etiology, as follows: type A, resulting from acute liver failure; type B, resulting from portosystemic shunt; and type C, resulting from liver cirrhosis.² HE, especially due to liver cirrhosis, is associated with significant mortality, reaching up to 64% at 1 year.³ In addition to the high mortality rate, HE imposes a great burden on various aspects of patient lives and healthcare systems.⁴ The management of HE starts with identifying and treating any precipitating cause, especially in patients with chronic liver diseases who may develop acute HE secondary to infection, bleeding, etc. Currently, several medications are utilized to treat HE, with a primary focus on decreasing ammonia production and absorption, such as by lactulose and rifaximin. Newer therapies are emerging and currently under study for the management of HE targeting traditional mechanisms of ammonia clearance in addition to novel mechanisms related to altering gut microbiome, reducing inflammation and oxidative stress, protecting endothelial integrity, and modifying neuronal responses (Fig. 1). In this article, we aim to review the management of HE, starting with the efficacy and limitations of traditional agents with a focus on the evidence supporting newer therapies in HE (Table 1).

Efficacy and limitations of traditional agents in management of HE

Lactulose and lactitol

Lactulose (beta-galactosidofructose) and lactitol (beta-galactosidosorbitol) are synthetic nonabsorbable disaccharides (NADs) that are given orally or rectally in patients with HE, in order to trap ammonia in the gut, thereby limiting intestinal absorption. Lactulose and lactitol are not absorbed due to the absence of a hydrolytic disaccharidase in the small intestine. This permits entry into the colon, where they undergo bacterial fermentation by colonic flora, resulting in an acidification of the luminal contents. Because of this acidity, ammonia (NH₃) is converted to ammonium (NH₄⁺) which cannot be absorbed, thus trapping ammonia within the colon and resulting in excretion in feces.^{5,6} In addition, the hyperosmolar properties of lactulose and lactitol exert cathartic effects which reduce gastrointestinal transit time available for ammonia absorption.⁷ Other potential mechanisms that have been described include increasing total fecal nitrogen excretion due to increased stool mass⁸ and reducing the formation of toxic fatty acids and ammo-

Keywords: Hepatic encephalopathy; Liver cirrhosis; Ammonia.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CGA-HE, Clinical Global Assessment of Hepatic Encephalopathy; CI, confidence interval; EASL, European Association for the Study of the Liver; FMT, fecal microbiota transplantation; GABA, gamma aminobutyric acid; GPB, glycerol phenylbutyrate; HAS, hepatic encephalopathy scoring algorithm; HE, hepatic encephalopathy; HR, hazard ratio; LOLA, L-ornithine L-aspartate; NAD, non-absorbable disaccharides; NNT, number needed to treat; OR, odds ratio; PAA, phenylacetic acid; PBA, phenylbutyric acid; PEG, polyethylene glycol; PHES, Psychometric HE-score; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCT, randomized clinical trial; RR, relative risk; SCFA, short-chain fatty acid; SOC, standard of care; TIPS, transjugular intrahepatic portosystemic shunt; WHS, West Haven scale.

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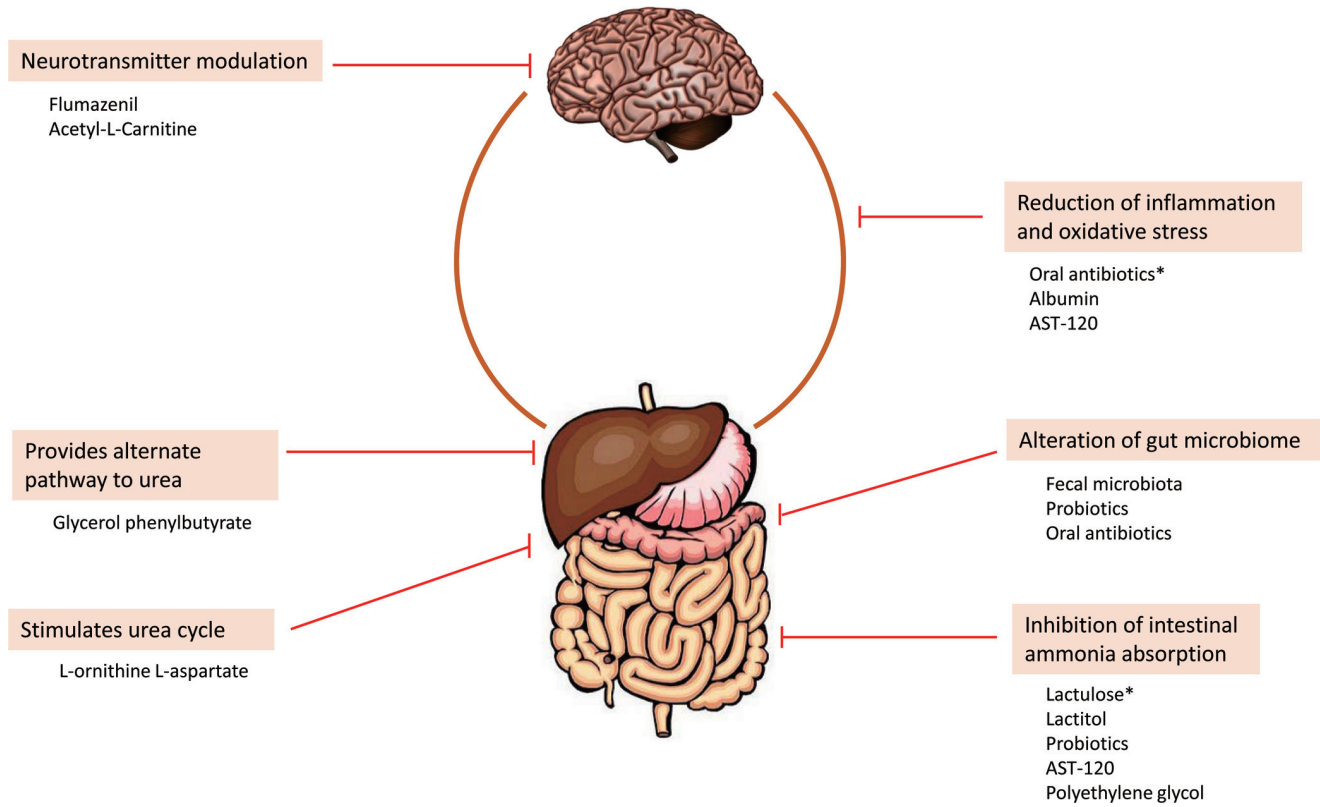


Fig. 1. Postulated mechanisms of medications used or being studied for treatment of hepatic encephalopathy. *These agents are approved by the U.S. Food and Drug Administration for the treatment of hepatic encephalopathy

nia in the colon.⁹ However, the most commonly used NADs to treat and prevent HE have been reported to have variable efficacy in randomized-controlled trials (RCTs).

In a recent systematic review and meta-analysis of RCTs (2016), treatment with NADs compared to placebo or no intervention was associated with improvement in HE in ~1/3 of patients (relative risk [RR]: 0.63, 95% confidence interval [CI]: 0.53-0.74, number needed to treat [NNT]: 4), and reduced mortality by half (RR: 0.49, 95% CI: 0.23-1.05, NNT: 100). These benefits were more pronounced in overt HE compared to minimal HE.¹⁰ Studies comparing lactulose to lactitol showed no differences in HE outcomes.^{11,12} Despite the consistent results showing benefit of NADs in reducing HE and its related mortality, these RCTs did not assess the confounding effect of factors precipitating HE since strategies directed at management of precipitating factors may improve HE with or without NADs. In addition, none of the prevention RCTs reported data on quality of life. Furthermore, the use of NADs was associated with increased risk of nonserious adverse events, such as bloating, diarrhea and nausea.¹⁰ These adverse events are likely to affect patient tolerability and compliance.^{13,14} In addition, the treatment effects on HE improvement (RR: 0.63) and mortality (RR: 0.49) from this meta-analysis indicate that a large proportion of patients with HE did improve despite treatment with NADs.¹⁰ Lactulose is Food and Drug Administration-approved and guideline-recommended (American Association for the Study of Liver Diseases [AASLD] 2014) for treatment and prevention of HE.

Oral antibiotics

Rifaximin is the most common oral antibiotic used to treat

and prevent HE, usually as an adjunct therapy added to NADs. Because rifaximin is minimally absorbed, it is concentrated in the gastrointestinal tract, which in turn alters gut microbiota composition and function, affects bile acid levels and composition, and exerts anti-inflammatory action and alters neurotoxin levels, all of which are implicated in the pathogenesis of cirrhosis complications.¹⁵ The efficacy of rifaximin was evaluated in a meta-analysis of five RCTs comparing rifaximin and NADs for treatment of HE. In that study, rifaximin had similar efficacy to NADs but with better tolerability.¹⁶ A subsequent placebo-controlled RCT evaluated the efficacy of rifaximin in prevention of future episodes of HE among patients with history of HE who were in remission. Compared to placebo, rifaximin reduced the incidence of breakthrough HE and future hospitalization involving HE by more than half.¹⁷ In that trial, however, more than 90% of patients received concomitant lactulose. A subsequent trial compared the efficacy of rifaximin plus lactulose vs. lactulose alone in resolution of overt HE. The combination therapy was more effective in reversal of HE (76% vs. 50.8%, *p*<0.004) and resulted in significant reduction of mortality (23.8% vs. 49.1%, *p*<0.05) and length of hospital stay (5.8±3.4 vs. 8.2±4.6 days, *p*=0.001). A subsequent, more recent meta-analysis confirmed the benefit of rifaximin in treatment and prevention of HE in addition to its benefit on mortality reduction.¹⁸ The 2014 Practice Guideline by the AASLD and the European Association for the Study of the Liver (EASL) recommended the use of rifaximin as an add-on therapy to lactulose for prevention of HE recurrence.¹⁹

There are multiple problems with the trials assessing the use of rifaximin,²⁰ such as confounding effects of transjugular intrahepatic portosystemic shunt (TIPS) and surgical

Table 1. Characteristics of novel agents for the treatment of HE

Agent	Mechanism of action	Current stage of research	Route and dose used in clinical studies	Methods of assessing neuropsychiatric outcomes used in clinical trials	Effect shown in clinical studies	Main limitations of published trials	Examples of ongoing trials in HE ^α
FMT	Altering gut microbiome by replacing potentially pathogenic taxa with beneficial, SCFA-producing taxa	Two phase 1 RCTs	90 cc enema once in one trial, and 15 FMT tablets once in the other trial	PHES, EncephalApp Stroop	No serious adverse events associated with the use of enema FMT, including no bacterial infections. - Enema FMT was associated with a reduced number of hospitalizations due to liver-related complications. Also, improvement in cognitive outcomes between baseline and post-treatment in the enema FMT group but none among those undergoing SOC. Oral FMT safe and well-tolerated, associated with enhanced microbial diversity, and favorable changes in antimicrobial protein expression and intestinal inflammatory markers, along with improved performance on cognitive scores	Enema FMT: small sample size; confounding effect of pre-FMT antibiotics; the control arm being SOC instead of placebo antibiotics or autologous FMT; short-term follow up; no significant change in microbiome diversity. Oral FMT: small sample design; single-blind design; low power to assess efficacy	NCT03420482, NCT03796598, NCT04014413
Probiotics	Reduction of ammonia-producing bacteria, and decreasing ammonia absorption in the gut	21 RCTs; 1 Cochrane systematic review and meta-analysis	Oral; variable	WHS, PHES, TMT, NCT, SDT, MRS, BAER	Compared to placebo, probiotics improve recovery and may lead to improvements in overt hepatic encephalopathy, quality of life, and plasma ammonia concentrations. No effect on all-cause mortality. No difference in adverse events. Compared to lactulose, benefit is uncertain due to limitations	High risk of bias. Outcome heterogeneity. Different types of probiotics used in different trials	NCT04787276, NCT04243148, NCT04175392, NCT03863730

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Table 1. (continued)

Agent	Mechanism of action	Current stage of research	Route and dose used in clinical studies	Methods of assessing neuropsychiatric outcomes used in clinical trials	Effect shown in clinical studies	Main limitations of published trials	Examples of ongoing trials in HE ^a
Albumin	Neutralizes reactive oxygen species, inhibits inflammatory mediators and reduces endothelial dysfunction and vasodilation	4 RCTs, meta-analysis of cohort and RCT	Short-term: 1-1.5 g/kg/day for 1-10 days. Long-term: 40 g twice weekly for 2 weeks, and then 40 g weekly for up to 18 months. Other: 20% albumin infusion up to 14 days or discharge to raise albumin level to ≥ 30 g/L	WHS	Initial trials and meta-analysis showed reduction in mortality, incidence of HE, HE recovery, hospital length of stay compared to placebo or standard of care. Recent trial (reference 54) showed no benefit of albumin over SOC when targeting albumin level ≥ 30 g/L	Open-label randomized trials. Most RCTs have small sample size. Non-blinding of outcome assessment. Cost effectiveness. Some trials with short-term follow-up	NCT03585257, NCT02401490
AST-120	Reduction of blood ammonia and oxidative stress by limiting absorption of neurotoxins and hepatotoxins	2 RCTs	Varied per trial; 6-12 (oral) sachets per day divided in 2-4 doses	WHS, HESA; RBANS, PHES, CGA-HE	Reduction of serum ammonia compared to placebo, reduction of diarrhea and flatulence compared to placebo. No difference on neurocognitive outcomes	Small number of patients. Study design allowed for improvement of neurocognitive outcomes even prior to randomization limiting its ability to detect true differences	None
Acetyl-L-carnitine	Reduction of serum ammonia by increasing ureagenesis; enhancement of neurotransmitter, protein and phospholipid synthesis	5 RCTs; 1 Cochrane systematic review and meta-analysis	2 g (oral) twice daily	TMT, SDMT, AVL, MMSE, EEG, BDI, STAI, VOT, Digit Cancellation Time, EMQ, COWAT, EEG, NPT	Individual studies showed improving neurological findings; reduction of serum ammonia level and improvement in performance on neuropsychological testing; improvement in energy levels, general functioning and well-being, and reduction of anxiety and depression; reduction of physical and mental "fatigue"; and improvement of cognitive deficits and EEG findings. Meta-analysis showed a reduction of blood ammonia among participants receiving acetyl-L-carnitine; however, the certainty of this finding was low due to limitations	Small number of participants, high risk of bias, and low power for detection of meaningful differences between the treatment groups; no reporting of mortality or serious adverse events between the groups	None

(continued)

Table 1. (continued)

Agent	Mechanism of action	Current stage of research	Route and dose used in clinical studies	Methods of assessing neuropsychiatric outcomes used in clinical trials	Effect shown in clinical studies	Main limitations of published trials	Examples of ongoing trials in HE ^a
GPB	Increased urinary excretion of ammonia	1 pilot study; 1 phase 1 RCT 2 RCT	6 mL (oral) twice daily	WHS	GPB reduced the number of patients with HE events, time to first event, total events, HE hospitalizations, and blood ammonia levels. Benefit was sustained after controlling for rifaximin use. No difference in serious adverse events between the two groups	Small sample size. More patients in the GPB group exited the study prematurely. 1/3 patients were taking rifaximin at the time of randomization	None
Flumazenil	Neurotransmitter modulation through competitive inhibition of GABA-A receptors	12 RCTs; 1 Cochrane systematic review and meta-analysis	Varied per trial; intravenous flumazenil at a total daily dose 0.2-6.5 mg	NCT, BAER, GCS, EEG, NPT	No on all-cause mortality, no difference in serious adverse events. Flumazenil was associated with improvement of HE	Small sample size in individual studies. High risk of bias Cross-over design; relapse rate not assessable. Short-term follow up	None
PEG	Reduce ammonia absorption by exerting a cathartic effect and reducing transit time	3 RCTs	4 L	HESA, WHS	PEG (alone or in combination with lactulose) is more effective than lactulose at improving HE at 24 h and associated with decreased length of stay. No difference in blood ammonia levels. No difference in serious adverse events	Small sample size. Single-center experiences. Non-blinding. Short-term follow up	NCT04436601, NCT03987893

^aClinicaltrials.gov website was searched for clinical trials relevant to hepatic encephalopathy and the agent of interest. AVL, auditory verbal learning test; BAER, brain-auditory evoked response; BDI, Beck depression inventory; COWAT, controlled oral word association test; EEG, electroencephalogram; EMQ, everyday memory questionnaire; MMSE, mini mental state examination; NCT, number connection test; NPT, neuropsychiatric test; SDMT, symbol digit modalities test; SDT, serial dotting test; STI, state trait anxiety inventory; TMT, trails making test; VOT, Hooper visual organization test.

portosystemic shunts,¹⁷ randomization imbalance,^{21,22} lack of benefit in high risk populations (such as in prevention of HE in those undergoing TIPS),²³ and absence of objective HE scales in outcome assessment in some of the studies.¹⁷ Despite these limitations, rifaximin is believed to be the best agent for use in combination with lactulose to maintain remission in patients with recurrent HE.¹⁹ Other antibiotics have been studied in management of HE; such as neomycin, metronidazole and vancomycin.^{24–27} Their use is limited by inconsistent data and concerns regarding toxicity and adverse effects.¹⁹ Rifaximin is Food and Drug Administration-approved and guideline-recommended (AASLD 2014) for treatment and prevention of HE.

L-ornithine L-aspartate (LOLA)

Ammonia detoxification is achieved by two main pathways in periportal hepatocytes: 1) urea synthesis in zone 1 and 2) glutamine synthesis in zone 3.²⁸ LOLA is a combination of endogenous amino acids that are metabolized in periportal and perivenous hepatocytes, where L-ornithine is utilized as a substrate in the urea cycle and acts as an activator of carbamoyl phosphate synthetase, the rate limiting enzyme of the urea cycle. Ammonia is also incorporated with glutamate to form glutamine catalyzed by glutamine synthase. The latter process also takes place in skeletal myocytes.²⁸ Multiple RCTs have studied the efficacy of intravenous and oral LOLA compared to placebo for treatment of HE (such as lactulose). Meta-analyses of these trials showed consistent reductions in ammonia levels and clinical improvement of HE.²⁹ Clinical trials assessing the efficacy of LOLA showed that it is at least comparable (sometimes superior) to other interventions (such as lactulose or oral antibiotics), in addition to being well-tolerated and associated with improvement in quality of life.^{29,30} Despite these benefits, the trials assessing the efficacy of LOLA suffer from several biases related to inadequate blinding, incomplete data, selective reporting, and pharmaceutical funding.³¹ In addition, there is no evidence to support the use of LOLA in patients with acute liver failure.³² LOLA is available and used routinely for management of HE in Europe. However, it is not available in the USA. Intravenous LOLA is not Food and Drug Administration-approved but is recommended by the guideline (AASLD 2014) as an alternative or additional agent for HE not responsive to conventional therapy.

Other therapies of HE

Mechanism of actions and critique of the evidence

Fecal microbiota transplantation (FMT): It has been shown that the gut microbial profile of cirrhotic patients with HE is different from those without HE or normal controls. Although this difference in the gut microbiome is in part driven by standard of therapy used in treatment of cirrhosis and HE (such as oral antibiotics, NADs, and acid suppressants) which can affect the gut microbiome composition,³³ cross-sectional data of stool metagenomics have revealed that certain metagenomic species are overexpressed or underexpressed in decompensated compared to compensated cirrhosis.³³ Additionally, gut dysbiosis has been shown to predict poor outcomes in HE.³⁴ Specifically, HE patients were found to have a lower prevalence of short-chain fatty acid (SCFA)-producing families, such as *Lachnospiraceae* and *Ruminococcaceae*, and increased prevalence of potentially pathogenic *Enterobacteriaceae*.^{34,35}

Using this microbial profile, Bajaj and colleagues³⁶ were

able to obtain stool specimens from a single healthy donor with the highest relative abundance of *Lachnospiraceae* and *Ruminococcaceae*. Frozen-then-thawed FMT units prepared from the single donor were instilled by enema and retained for 30 m in patients with HE after a 5-day course of broad spectrum antibiotics (metronidazole, ciprofloxacin, and amoxicillin) aimed to decrease host bacterial burden and make the colonic environment more receptive to colonization from the donor microbiota. In this safety and open-label RCT involving 20 patients with cirrhosis and recurrent HE, who were randomized 1:1 to either FMT or standard-of-care (including lactulose and rifaximin), there was no serious adverse event associated with the use of FMT, including no bacterial infections. Additionally, the FMT was associated with a reduced number of hospitalizations due to liver-related complications, and there was a significant improvement in cognitive outcomes between baseline and post-treatment in the FMT group but none among those undergoing standard of care (SOC). This trial had several limitations, including a small sample size, confounding effect of pre-FMT antibiotics, control arm being SOC instead of placebo antibiotics or autologous FMT, and short-term follow up (up to 20 days). Additionally, there was no significant change in microbiome diversity, as assessed by 16S rRNA sequencing.³⁶

In another phase 1, randomized, single-blind, placebo-controlled safety trial, Bajaj and colleagues³⁷ studied the use of oral FMT capsules in patients with cirrhosis and recurrent HE. FMT capsules were prepared from the same healthy donor with the relative high abundance of *Lachnospiraceae* and *Ruminococcaceae* used in their previous enema trial, and were given at a dose of 15 capsules at one time. This trial was unique because all subjects underwent esophagogastroduodenoscopy and sigmoidoscopy for mucosal biopsies before and after FMT treatment. Twenty patients already on lactulose/rifaximin were enrolled (randomized 1:1 to either FMT capsules or placebo capsules); FMT appeared to be safe, well-tolerated and associated with enhanced microbial diversity, and to provide favorable changes in antimicrobial protein expression and intestinal inflammatory markers, along with improved performance on cognitive scores. Another, ongoing phase 2 RCT is underway to further investigate the safety and benefit of aggressive gut microbial manipulation using FMT oral capsules.³⁸ At this time, FMT is not Food and Drug Administration-approved nor mentioned by the guidelines (AASLD 2014) yet as a treatment in HE.

Probiotics

A probiotic is conventionally defined as “a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host”.^{39,40} Although probiotics are often bacterial microorganisms, most commonly *Lactobacillus* or *Bifidobacterium*, yeasts are also used. Because of the variety of microorganisms in probiotics, various species or strains may confer a variety of health benefits, and disease-specific probiotics exist. In HE, as discussed above, it has been shown that the alteration of gut microbiome plays an important role in neurocognitive outcomes in patients with cirrhosis. Probiotics are hypothesized to benefit patients with HE through reduction of harmful, ammonia-producing bacteria, and decreasing ammonia absorption in the gut by affecting different aspects of the gastrointestinal environment (including enzymatic composition, epithelial permeability, acidic environment and nutritional status of the gut).⁴¹

Evidence supporting the use of probiotics in HE comes

from a comprehensive Cochrane systematic review and meta-analysis of 21 trials published prior to June, 2016 involving 1,420 patients comparing a probiotic to either placebo (14 trials) or lactulose (7 trials). When probiotics were compared to placebo or no treatment, this review found no effect in all-cause mortality. However, there was moderate-quality evidence that probiotics improve recovery and may lead to improvements in overt HE, quality of life, and plasma ammonia concentrations. When antibiotics were compared to lactulose, the benefits were uncertain because of the very low-quality evidence. Importantly, no reports of septicemia related to the use of probiotics were found.⁴¹ The review highlighted several limitations in the included trials, including high risk of bias, outcome heterogeneity, and different types of probiotics used.⁴¹ In these studies, VSL#3 (containing four species of *Lactobacilli*, three of *Bifidobacteria* and *Streptococcus thermophilus*) was the most commonly used probiotic product in the clinical trials. Probiotics use in HE remains under study and multiple clinical trials assessing other strains are underway to investigate its benefits in patients with cirrhosis.^{42–45} At this time, probiotics are not Food and Drug Administration-approved nor guideline-recommended (AASLD 2014) for the treatment of HE, though they are mentioned as possible alternative therapy pending further study.

Albumin

Synthesized in the liver, albumin is known to decrease in patients with progressive liver disease and cirrhosis. Intravenous albumin administration has been shown in experimental studies to neutralize oxygen-reactive species, inhibit inflammatory mediators and reduce endothelial dysfunction and vasodilation in patients with liver cirrhosis, in addition to its oncotic, volume-expanding effect on the circulation^{46–48} in patients with cirrhosis. Albumin has been shown to improve response to diuretics, prevent circulatory dysfunction after large-volume paracentesis and to have a role in prevention and treatment of hepatorenal syndrome.⁴⁹ The benefit of albumin administration in the prevention and treatment of HE was studied in few clinical trials with promising results.

A multicenter, double-blind small RCT involving 56 cirrhotic patients with acute HE who had been randomized to receive intravenous albumin (1.5 g/kg on day 1 and 1.0 g/kg on day 3) vs. isotonic saline, in addition to usual treatment (laxatives and oral antibiotics), showed that there was no significant differences in the percentage of patients with short-term resolution of HE (at day 4). However, there was a significant reduction in mortality at day 90 (69.2% vs. 40%, $p=0.02$).⁵⁰ In 2017, Sharma and colleagues⁵¹ randomized 120 patients with overt HE to receive lactulose (30–60 mL three times a day; goal 2–3 semisoft stools per day) plus albumin (1.5 g/kg/day) or lactulose alone, and treatment was continued until recovery of HE or for a maximum of 10 days. The combination therapy resulted in more patients achieving complete recovery of HE by day 10, as assessed by West Haven scale (WHS) (75% vs. 53.3%, $p=0.03$), shorter hospital stay 6.4 ± 3.4 vs. 8.6 ± 4.3 days, $p=0.01$, lower mortality (18.3% vs. 31.6%, $p=0.04$), in addition to significant reductions in levels of IL-6, IL-18, TNF-alpha and endotoxins but not levels of arterial ammonia. There was no difference in side effects related to drug therapy. The main limitations of that study included the small sample size, open-label design, and absence of concomitant rifaximin use, which is known to reduce short-term mortality.

The value of long-term albumin administration was investigated in the ANSWER study, a multicenter, randomized, open-label trial that assigned 440 patients with cirrhosis

and uncomplicated ascites resistant to diuretic therapy to receive either standard medical therapy or standard medical therapy plus albumin (40 g twice weekly for 2 weeks, and then 40 g weekly) for up to 18 months. Although HE assessment was not the main goal in that study, it was assessed as a secondary end point. At the study completion, 18-month survival was higher in the standard medical therapy plus albumin group (77% vs. 66%, $p=0.028$), and there was decreased incidence in grade 3–4 HE (odds ratio: 0.48, 95% CI: 0.37–0.63, $p<0.001$). In addition, albumin treatment decreased the future need for therapeutic paracentesis, renal dysfunction, hyponatremia, hyperkalemia, bacterial infections, hepato-renal syndrome, and hospital length of stay.⁵² Given the concerns regarding costs of albumin administration, cost-effective analysis in that study showed a favorable cost-effective ratio, likely attributed to better quality of life and fewer hospital admissions in the albumin group. Despite its impressive results, the study had several limitations, the main being its open-label design, which may have led to patients receiving albumin to be seen more frequently than patients in the other group. Additionally, although outcome assessors were from an independent non-profit consortium, they were not blinded to the treatment allocations and may have introduced bias. A more recent, single-center retrospective propensity-matched analysis involving 2,868 patients and meta-analysis of nine cohort and prospective trials showed that albumin administration was associated with reduced incidence and improvement of overt HE in addition to lowering in-hospital mortality.⁵³

Another recent, randomized, multicenter, open-label trial was conducted in the UK and studied whether targeting an albumin serum level ≥ 30 g/L would reduce the risk of infections, renal dysfunction and death in patients with decompensated cirrhosis.⁵⁴ In that study, 777 patients hospitalized with decompensated cirrhosis (~20% of which admitted for HE) and serum albumin <30 g/L were randomized to receive daily infusions of 20% albumin for 14 days or until discharge (whichever comes first) vs. SOC; patients in the SOC group were allowed to receive albumin infusions when indicated (such as hepatorenal syndrome, peritonitis or large-volume paracentesis). At the conclusion of the trial, the primary end-point (new infection, kidney dysfunction, or death between days 3 and 15 after the initiation of treatment) did not differ significantly between the groups (adjusted odds ratio: 0.98; 95% CI 0.71–1.33). Furthermore, subgroup analysis of the primary outcome in those hospitalized for HE did not reveal significant benefit (adjusted OR 0.91; 95% CI 0.44–1.86). The study concluded that targeting albumin level ≥ 30 g/L is not beneficial compared to SOC in patients with decompensated cirrhosis, and called into question the utility of albumin in patients with decompensated cirrhosis; however, it was limited mainly by its open-label design and short-term follow up. Albumin is currently being evaluated in other ongoing trials.^{55–57} At this time, albumin is not Food and Drug Administration-approved nor guideline-recommended (AASLD 2014) for the treatment of HE, though it is mentioned as possible alternative therapy pending further study.

AST-120

AST-120 is a synthetic activated carbon microsphere that has a large surface area with a high nonspecific adsorptive capacity. AST-120 has limited gastrointestinal absorption, which adds to its ability to trap neurotoxins and hepatotoxins in the gut.⁵⁸ The ability of AST-120 to reduce blood ammonia levels and reduce oxidative stress has been shown previously in rat models of cirrhosis^{58,59} and renal failure.⁶⁰ AST-120 was studied in a phase-2, multicenter RCT that

evaluated the efficacy and safety of AST-120 in the treatment of low-grade HE. The study included 41 patients who were randomized to receive either AST-120 (2 g sachets four-times per day) or lactulose (titrated to 2–3 soft stools per day) for 4 weeks. The primary end-point was defined as ≥ 1 -point reduction in the WHS of HE over 4 weeks. Secondary endpoints were changes in the Hepatic Encephalopathy Scoring Algorithm (HESA), venous ammonia, and tolerability. At the study completion, the primary endpoint at week 4 was similar between treatment groups (38.1% vs. 35.0%, AST-120 vs. lactulose); secondary endpoints were also similar. However, diarrhea and flatulence occurred less frequently in the AST-120 group.^{61,62} One of the major limitations of this study was the low number of patients and the absence of a placebo arm, prompting a placebo-controlled “AST-120 Used to Treat Mild Hepatic Encephalopathy” (ASTUTE) clinical trial,⁶³ a multicenter, double-blind RCT that randomized 148 patients with compensated cirrhosis to receive either dose-ranging oral AST-120 (2 or 4 g three times per day) vs. placebo.⁶⁴ The primary endpoint was neurocognitive improvement defined as a change in the global summary score of Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at 8 weeks compared to baseline; secondary endpoints included Psychometric HE-score (PHES), Clinical Global Assessment of HE (CGA-HE), and frequency of occurrences of overt HE and hospitalization. At study completion, there was no difference in RBANS scores between baseline and 8 weeks for all groups, and there were no differences in secondary endpoints. However, all groups had improvement in RBANS score between the time of screening and baseline visits (at 1 week), even before randomization. Thus, the study was strongly confounded by its design, allowing for improvement in neurocognitive scores prior to randomization. Interestingly, venous ammonia levels significantly improved in treatment groups (but not in placebo) independently of neurocognitive changes.^{63,64}

At the time of this article preparation, there are no known ongoing clinical trials evaluating the use of AST-120 for the treatment of HE. AST-120 is currently being used and actively studied in treatment of progressive of chronic kidney disease.⁶⁵ At this time, AST-120 is not Food and Drug Administration-approved nor guideline-recommended (AASLD 2014) for the treatment of HE.

Acetyl-L-carnitine

Carnitine is an essential nutrient that is important for fatty acid transfer across the inner mitochondrial membrane, especially in hepatocytes.⁶⁶ The metabolism of carnitine has been shown to be impaired (and serum carnitine levels reduced) in patients with chronic liver diseases. Acetyl-L-carnitine is an ester of carnitine that is endogenously produced within mitochondria and peroxisomes in the liver, brain and kidney by the enzyme acetyl-L-carnitine transferase.⁶⁷ The role of acetyl-L-carnitine in the treatment of HE is postulated to be related to reduction of serum ammonia by increasing ureagenesis⁶⁷ in addition to enhancing the production of acetylcholine in the brain (by facilitating the uptake of acetyl-coenzyme A) and stimulating protein and phospholipid synthesis, all of which increase cellular energy production and reduce neuronal toxicity in patients with HE.^{66,67}

Most of the data on the use of acetyl-L-carnitine comes from small RCTs; although, the individual RCTs suggested a benefit of acetyl-L-carnitine compared to placebo in improving neurological findings.⁶⁸ Reduction of serum ammonia level and improvement in performance on neuropsychological testing,⁶⁹ improvement in energy levels, general functioning and well-being, and reduction of anxiety and depression,⁷⁰ reduction of physical and mental “fatigue”,⁷¹ and

improvement of cognitive deficits and EEG findings⁷¹ in these studies were limited by small number of participants, high risk of bias, and low power for detection of meaningful differences between the treatment groups. A recent Cochrane systematic review and meta-analysis assessing these five RCTs that collectively randomized 398 participants to oral or intravenous acetyl-L-carnitine vs. placebo concluded the studies to be underpowered for the treatment effect, with a high risk of bias.⁷² Meta-analysis of these trials showed a reduction of blood ammonia among participants receiving acetyl-L-carnitine. However, the certainty of this finding was low due to limitations in study design and execution of the trials. Importantly, none of these trials assessed all-cause mortality and differences in serious adverse events. Adverse events of acetyl-L-carnitine were poorly reported, making the potential harms of acetyl-L-carnitine remain currently unknown.⁷² More highly powered and adequately designed clinical trials are needed to assess the efficacy and safety of acetyl-L-carnitine compared to placebo and current standard of therapy prior to the implementation of its widespread use. At this time, acetyl-L-carnitine is not Food and Drug Administration-approved nor guideline-recommended (AASLD 2014) for the treatment of HE.

Glycerol phenylbutyrate (GPB)

GPB is a nitrogen-binding agent consisting of three phenylbutyric acid (PBA) molecules joined to glycerol by an ester linkage. It is currently approved in the USA and Europe for use in urea cycle disorders in patients with chronic hyperammonemia who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.^{73–76} Phenylacetic acid (PAA), the major metabolite of PBA, is conjugated with glutamine (which contains two molecules of nitrogen) by acetylation in the liver and kidneys to form phenylacetylglutamine (PAGN) which is easily excreted by the kidneys, providing an alternate vehicle for nitrogen waste excretion and reducing blood ammonia level.^{74,76,77} A pilot, open-label dose-ranging study involving 15 patients with cirrhosis and HE patients showed that oral GPB (6 mL twice a day) was tolerated and resulted in significant lowering of blood ammonia concentrations.⁷⁸ This study was followed by a phase 2, randomized, double-blind trial enrolling 178 cirrhosis patients with history of recurrent HE who received either GPB (6 mL twice daily for 16 weeks) vs. placebo (1:1 randomization). Compared to placebo, GPB reduced the number of patients with HE events (21% vs. 36%, $p=0.02$), time to first event (hazard ratio [HR]=0.56, $p<0.05$), total events (35 vs. 57, $p=0.04$), HE hospitalizations (13 vs. 25, $p=0.06$), and blood ammonia levels ($p=0.04$).⁷⁹ There was no difference in serious adverse events between the two groups. The study was limited by small sample size, and more patients in the GPB group exited the study prematurely, which could result in a lower HE event rate in the treatment arm. However, the authors showed that the treatment effect remained in a time-to-event survival analysis performed to account for dropouts.⁷⁹ Additionally, 59 patients (33%) were taking rifaximin at the time of randomization, likely indicating more refractory disease. However, the treatment benefit was sustained after controlling for rifaximin use. At this time, GPB is not Food and Drug Administration-approved nor guideline-recommended (AASLD 2014) for the treatment of HE, though it is mentioned as possible alternative therapy pending further study.

Flumazenil

Flumazenil is a competitive inhibitor at the benzodiazepine

binding site on the gamma aminobutyric acid (GABA)-A receptor. It is most commonly used in benzodiazepine overdose and reversal of anesthesia.⁸⁰ Several studies have shown that patients with HE have an up-regulation of GABA-A receptors and increased GABAergic tone.^{81,82} Because GABA is the main inhibitory neurotransmitter in the central nervous system, this upregulation of GABAergic neurons is postulated to be responsible, at least in part, for the neurocognitive manifestations of HE. A number of clinical trials assessed the effects of flumazenil in patients with HE. However, these trials were individually relatively small and included cross-over designs that limited the interpretability of clinically meaningful outcomes.⁸³ A Cochrane systematic review and meta-analysis of 12 RCTs involving 842 patients comparing flumazenil vs. placebo reported that there was no effect of flumazenil on all-cause mortality. However, flumazenil was associated with an improvement of HE, and with no difference in serious adverse events. The main limitation of these studies was the short follow-up time which ranged from a few minutes to 2 weeks in these trials. However, follow up was less than 1 day in the majority of the studies, limiting any overreaching conclusions about the benefit of flumazenil on long-term cognitive outcomes.⁸³ Other limitations include high risk of bias in the majority of the studies, and cross-over designs in individual studies limiting the ability to estimate the risk of HE relapse.⁸³ Because of this limited duration of action and no effect on mortality, flumazenil is not routinely used for the treatment of HE until warranted by further trial data. At this time, flumazenil is not Food and Drug Administration-approved nor guideline-recommended (AASLD 2014) for the treatment of HE, though it is mentioned as possible therapy in select cases pending further study.

Polyethylene glycol

Polyethylene glycol 3350-electrolyte solution (PEG) is a cathartic agent postulated to improve outcomes in HE by reducing gastrointestinal transit time available for ammonia absorption. This cathartic effect is somewhat similar to that exerted by NADs due to their unabsorbed hyperosmolar characteristics. However, unlike lactulose and lactitol, PEG does not have the carbohydrate load that reduces stool pH and is not metabolized by colonic bacteria.⁸⁴ Published in 2014, the HELP study (Hepatic Encephalopathy: Lactulose vs. Polyethylene Glycol 3350-Electrolyte Solution) was the first RCT to compare PEG (4-L dose) vs. lactulose in 50 patients with cirrhosis admitted for HE. PEG was found to be associated with a higher incidence of HE improvement assessed by improvement in HESA scores at 24 h (91% vs. 52%, $p < 0.01$), and with a shorter median time to improvement in HE (1 vs. 2 days, $p = 0.01$). There was no difference in serious adverse events, although the PEG group experienced more diarrhea and the lactulose group experienced more bloating.⁸⁵ Ammonia levels in that study did not correlate with improvement in HE scores.

A more recent RCT similarly compared PEG with lactulose for treatment of overt HE in 100 patients with post-hepatitis C cirrhosis admitted for HE. At study completion, PEG was associated with a higher incidence of HE improvement on HESA scores compared to lactulose (94% vs. 72%), along with a reduced time needed for HE resolution and length of hospital stay, and no differences in serious adverse events.⁸⁶ Combining lactulose with PEG might be helpful, which was assessed in a non-inferiority trial that randomized 40 patients with cirrhosis and HE to receive either lactulose alone (20–30 g orally or 200 g enema) or a similar dose of lactulose plus PEG (280 g in 4 L of water orally as a single dose in 30–120 m). Combination therapy (PEG plus lactulose) was

more effective than lactulose alone in improving HESA scores at 24 h and was associated with reduced length of hospital stay and with no significant differences in blood ammonia levels or serious adverse events.⁸⁷ The main limitations of these trials include the small sample size, being limited to single-center experiences, non-blinding of the studies, and absence of long-term outcomes. There are multiple ongoing trials assessing the benefit of PEG in HE.^{88,89} At this time, polyethylene glycol is not Food and Drug Administration-approved nor guideline-recommended (AASLD 2014) for the treatment of HE, though it is mentioned as possible alternative therapy pending further study.

Agents such as L-ornithine phenyl acetate, sodium benzoate, and zinc have been studied but lack sufficient evidence of efficacy to be recommended.^{90–92}

Conclusions

The management of HE is complex and requires clinicians to be updated on the most recent advances in prevention and treatment. Older therapies (such as NADs and oral antibiotics) remain the first line of treatment according to current guidelines. However, multiple new agents have been developed and are being used for the treatment of HE. These agents are in various stages of research and some require further study prior to routine use in clinical practice. Because of several limitations in the existing literature, future research should focus on large-scale clinical trials with adequate design, sample size, elimination of biases, reporting of adverse events, and standardization of treatment outcomes.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

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