Important Unresolved Questions in the Management of Hepatic Encephalopathy: An ISHEN Consensus

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Management of hepatic encephalopathy (HE) remains challenging from a medical and psychosocial perspective. Members of the International Society for Hepatic Encephalopathy and Nitrogen Metabolism recognized 5 key unresolved questions in HE management focused on (i) driving, (ii) ammonia levels in clinical practice, (iii) testing strategies for covert or minimal HE, (iv) therapeutic options, and (v) nutrition and patient-reported outcomes. The consensus document addresses these topical issues with a succinct review of the literature and statements that critically evaluate the current science and practice, laying the groundwork for future investigations.

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INTRODUCTION

The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) has a global clinical, basic, and translational membership. Clinically-oriented members of the ISHEN Executive Committee, Organizing Committee, and other prominent clinical physician researchers were challenged to come up with the top questions that would be relevant for day-to-day management of patients who have experienced covert or overt hepatic encephalopathy (HE). These were then collated, and ultimately, the top 5 topics were coalesced into (i) driving impairment, (ii) clinical use of ammonia levels, (iii) diagnosis of minimal/covert HE (MHE/CHE), (iv) treatment strategies, and (v) nutrition and patient-reported outcomes (PROs). All statements were discussed by the ISHEN Executive Committee and within the authorship and are shown in Table 1. Differences of opinion were addressed face to face and via e-mail, and all authors agreed on this document.

HE AND FITNESS TO DRIVE

A decline in cognitive function results in a higher risk of traffic accidents regardless of the cause for the cognitive decline (1). On-road driving tests have shown that patients with cirrhosis and HE have problems with car handling, adaptation, cautiousness, keeping in lane, and brake usage and that they more often need intervention from an instructor to avoid accidents (2,3). These real-life findings are supported by studies using driving simulation (4,5). Epidemiologic studies confirm that patients with cirrhosis with cognitive impairment have more traffic accidents and violations compared with unimpaired patients with cirrhosis (6). Patients with MHE tend to overestimate their driving skills (3,7). Treatments seem to improve driving simulator performance (8). Of note, a couple of studies have found no increased accident rate in MHE (9,10). Physicians are not trained to assess fitness to drive, and no simple psychometric test has the ability to reliably divide patients into safe and unsafe drivers, i.e., only half of patients with MHE seem to be poor drivers in real life (11). Legal ramifications differ widely, but most patients with HE experience lapses of consciousness during the recent or current overt HE (OHE) phase (12). Currently, no clear guidelines exist for restricting driving in patients with MHE/CHE with or without recent OHE, but restrictions within 3 months of an OHE episode are from an expert consensus (13) (Figure 1). In addition, different jurisdictions within and between countries have different regulatory and legal approaches, and clinicians should be aware of their responsibilities. In the United States, https://one.nhtsa.gov/people/injury/olddrive/OlderDriversBook/pages/Contents.html contains the links.

Consensus statements

1. A short objective and nonjudgmental driving history should be taken at each visit (Do you drive? Have you had accidents or "near-misses"?).
2. Special care should be taken to cognitively evaluate patients with cirrhosis who are active drivers and/or have recently (<3 months) had an episode of OHE.
3. Cognitive testing alone is not specific enough to determine who is a poor driver and should not be used alone to restrict driving.
4. In those with recent (<3 months) episode(s) of OHE, oral and written advice to avoid driving should be given to patients and caregivers based on expert consensus.
5. In case the affected patients want to resume driving, they should schedule a formal driving reassessment with the local authorities based on local regulations.

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Table 1. Consensus statements

Topic	Statements
Driving and HE	A short objective and nonjudgmental driving history should be taken at each visit (Do you drive? Have you had accidents or near-misses?).
	Special care should be taken to cognitively evaluate patients with cirrhosis who are active drivers and/or have recently (<3 mo) had an episode of overt hepatic encephalopathy.
	Cognitive testing alone is not specific enough to determine who is a poor driver and should not be used alone to restrict driving.
	In those with recent (<3 mo) episode(s) of overt HE, oral and written advice to avoid driving should be given to patients and caregivers based on expert consensus.
	In case the affected patients want to resume driving, they should schedule a formal driving reassessment with the local authorities based on local regulations.
	The physician should be familiar with local legislation regarding mandatory reporting to local traffic authorities.
Ammonia levels in clinical practice	Ammonia levels should not be prioritized over the clinical examination for the diagnosis and staging of hepatic encephalopathy
	Ammonia draws should be carefully timed and logistically planned to exclude false-positive values
	A normal ammonia level in a patient with cirrhosis who is overtly confused should alert the provider to diagnoses other than HE
	Isolated ammonia level increases without accompanying clinical signs or symptoms of HE should not alone be an indication for clinical therapy.
Diagnosis and testing for MHE/CHE	Diagnosis of MHE/CHE should be based on a patient's performance on neuropsychological tests that are nationally and culturally validated, following availability and local expertise.
	The combination of 2 or more tests to establish the diagnosis of MHE/CHE is discouraged. Although such practice would theoretically improve diagnostic accuracy, there is no clinical rationale or available evidence to substantiate it, and it unnecessarily decreases the prevalence of the disease without improving its predictive usefulness.
	Screening for MHE/CHE could ideally be offered to all patients with cirrhosis, but until point-of-care tests with widespread validation and links to outcomes are available, MHE screening can be restricted to targeted populations where fitness to work or drive is questioned or when prompted by specific symptoms.
	Neuropsychological tests, such as PHES, CFF, CRT, EncephalApp, and ANT have had validation and could be recommended for investigating MHE/CHE.
Treatment of HE	CHE/MHE therapy
	Once CHE/MHE is diagnosed, these patients are prone to develop overt HE; hence, therapy can be considered on a case-by-case basis.
	Lactulose could be recommended for treating minimal HE as a trial run in those whom testing is positive.
	OHE acute episode
	Identify and treat precipitating factors for HE.
	Lactulose is the first choice for treatment of overt HE by enema or oral route based on severity of HE. Lactulose is recommended for secondary prophylaxis after the first episode
	IV LOLA can be used as an alternative or additional agent to treat patients nonresponsive to lactulose.
	Polyethylene glycol can also be used in case of ileus or prior intolerance to lactulose or based on local preference
	Prevention of recurrence
	Lactulose is recommended for prevention of recurrence of overt HE episode(s) after the initial episode.
	Rifaximin is recommended as an add-on to lactulose for prevention of recurrent episodes of overt HE after the second episode
Nutrition and PROs	In patients with cirrhosis and HE, BCAA supplementation should be considered for the prevention of HE recurrence, especially if dietary protein intake is inadequate.

Table 1. (*continued*)

Topic	Statements
	Clinical teams should aim toward providing personalized and practical dietary counseling around how to achieve guideline-based calorie targets, protein targets, and eat frequent meals and snacks to avoid prolonged periods of fasting for all patients with cirrhosis and HE.
	Protein restriction should be avoided in patients with HE.
	HE has a profound impact on both patients and caregivers.
	Efforts should be made to elicit patient-reported and caregiver-reported outcomes at diagnosis and intermittently over time to determine when optimization of therapy or additional supports may be required.

ANT, animal naming test; BCAA, branched-chain amino acid; CFF, critical flicker frequency; CHE, covert HE; CRT, continuous reaction time; HE, hepatic encephalopathy; LOLA, L-ornithine-L-aspartate; MHE, minimal HE; PHES, psychometric hepatic encephalopathy score; PRO, patient-reported outcome.

6. The physician should be familiar with local legislation regarding mandatory reporting to local traffic authorities.

AMMONIA LEVELS IN CLINICAL PRACTICE

Ammonia plays a central role in the pathophysiology of HE but has an unclear role in clinical practice. In this section, we review the current use of ammonia levels in the diagnosis and management of patients with liver disease. There are several caveats to the optimal ammonia blood draw and its interpretation. Ideal ammonia blood draw settings should be as follows. There is probably limited advantage in measuring arterial compared with venous ammonia levels, which can be considered acceptable (14,15). Venous blood should be preferably drawn when the patients is fasting, in a tube with a stabilizer, refrigerated on ice instantaneously, sent to the laboratory, and analyzed immediately, preferably within 30–60 minutes. If arterial or capillary ammonia is used, the appropriate reference values should be obtained and used. Capillary ammonia is best measured on blood obtained from the earlobe, as sweat artifact leads to significant overestimation on blood drawn from the fingertip (16,17).

Diagnosis of HE

Blood ammonia is often used to diagnose or guide treatment in HE (18). In survey studies, irrespective of clinical subspecialty, clinicians report frequent use of and belief in the utility of ammonia levels to diagnose HE (18,19). In a single-center study from the United States, 95% of patients with HE received ammonia testing (20). Although there is a direct correlation of ammonia with the severity of HE in acute liver failure (21), this is not the case in patients with cirrhosis. Indeed, hyperammonemia may be present in the absence of any clinical evidence of HE, and ammonia levels are actually normal in up to 60% of patients with cirrhosis presenting to an emergency department with mental confusion (22,23). One major reason is that infection and systemic inflammation (24) have also been shown to be associated with the development of grade 3/4 HE (25) and can cause confusion/delirium also in patients without liver disease (i.e., septic encephalopathy). Although hyperammonemia may be insufficient to cause HE in cirrhosis alone, normal ammonia levels in a confused patient with cirrhosis should direct investigations toward an alternative diagnosis (26). It should also be noted that valproic acid may cause hyperammonemia and must be considered when interpreting ammonia levels and especially when mental confusion ensues in a patient on this treatment, although the use of valproate is rare in this population.

Staging of HE

For a given population of patients with cirrhosis and HE, the ammonia level trends with the severity of the episode, and there is substantial overlap between grades of HE such that there is no absolute value that discerns severity (23,27–29). Ammonia levels will also fluctuate within a given 24-hour period, and ammonia levels will rise following a high-protein meal (29), prolonged fasting (muscle breakdown), gastrointestinal bleeding, intense physical activity, transjugular intrahepatic portosystemic shunt (TIPS), and in the context of reduced renal function (30); levels drop with an increase in urinary ammonia excretion following a fluid challenge (31). Therefore, clinical use and interpretation of ammonia levels must take these logistic issues into consideration (Figure 2) (32). Ammonia levels have high negative predictive value. Normal ammonia in a patient with confusion/coma should prompt a differential diagnosis pathway focusing on diseases other than HE. There is no definite role for serial measurement of ammonia levels, but this type of information might help in case of a dissociation between the clinical phenotype and ammonia levels in the course of time.

Guiding the therapy of HE

Ammonia levels are frequently ordered to guide the efficacy of therapy. Unfortunately, ammonia levels often remain elevated or even unchanged after resolution of either an overt or covert episode (22,33). Although ammonia levels may fall during therapy, they are unlikely to normalize (34). Notably, if specific therapies are primarily directed toward plasma ammonia levels, guiding those therapies during clinical trials may necessitate repeated ammonia evaluation.

Prognosis of HE

Hyperammonemia is associated with increased mortality adjusting for severity of illness with higher baseline ammonia predicting hospitalizations and breakthrough episodes (35–39). Ammonia is cytotoxic, impairing neutrophil function in liver disease (40), and paradoxically induces immune dysfunction, which may further exacerbate HE (41). Prospective data are needed to determine whether ammonia level determination improves prognostication independent of the clinical signs and symptoms of HE (36–38).

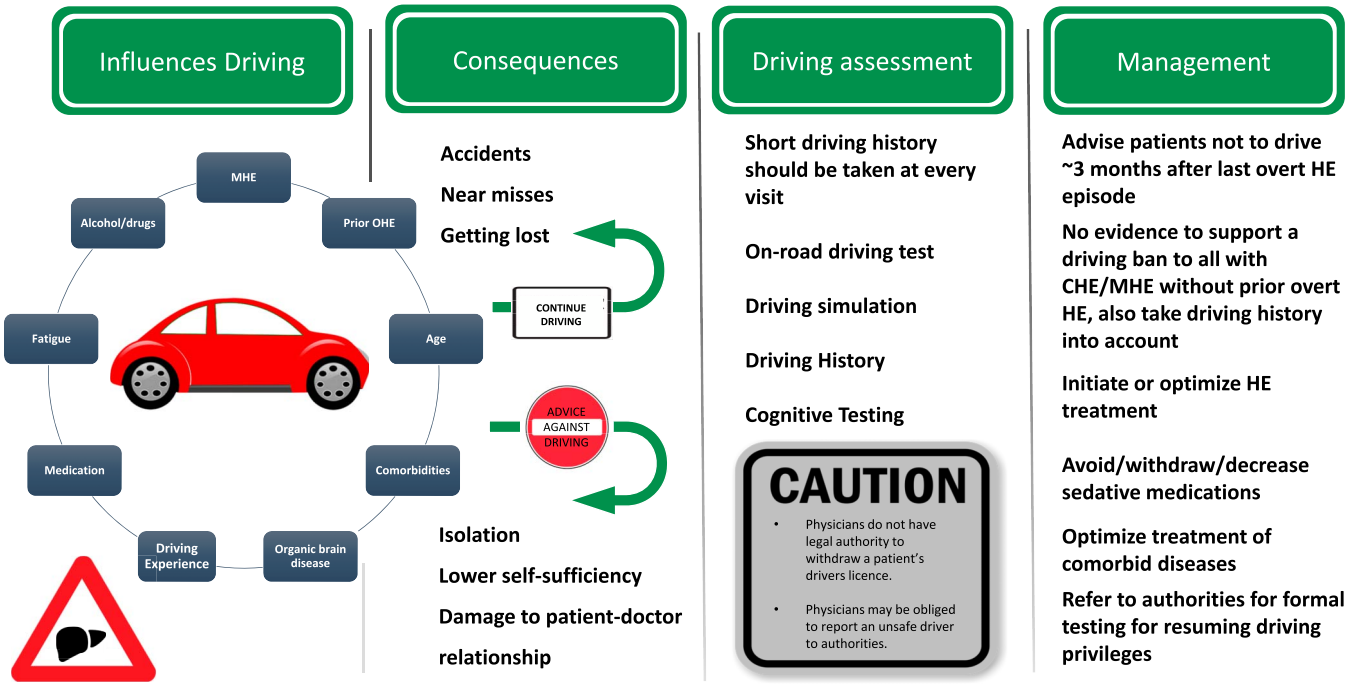

Figure 1. Overview of contributing factors, consequences, and management of driving impairment in hepatic encephalopathy.

MHE/CHE TESTING

MHE can only be identified through neuropsychological or neurophysiological testing. The difficulties associated with the clinical diagnosis of grade I HE, which is heavily operator dependent and difficult to compare between centers, have resulted in a proposal to combine MHE and grade I HE and qualify them as CHE (42,43). MHE/CHE is relevant to identify because it is associated with impaired PROs (44,45), functional decline and falls (46,47), motor vehicle accidents (11,48), caregiver burden (49), and a higher risk of subsequent OHE development.

Neuropsychological and neurophysiological tests are used to investigate MHE/CHE. A number of tests and test batteries have been validated for this purpose (50). Whereas cross-sectional validation uses a reference population to contrast observed and expected results, the optimal studies are longitudinal and use a clinical outcome as the end point for validation (51). Tables 2 and 3 summarize some key cross-sectional and longitudinal studies with commonly used tests. These studies have contributed to the progress in the field, particularly regarding the recognition of (i) need for adjustment for age/sex, education, and nationally /culturally validated tests, (ii) varied prevalence depending on tests used or their combinations, (iii) lack of agreement among available tests, (iv) relevance of MHE/CHE as a prognostic factor, and (v) identification of MHE/CHE as a therapeutic target.

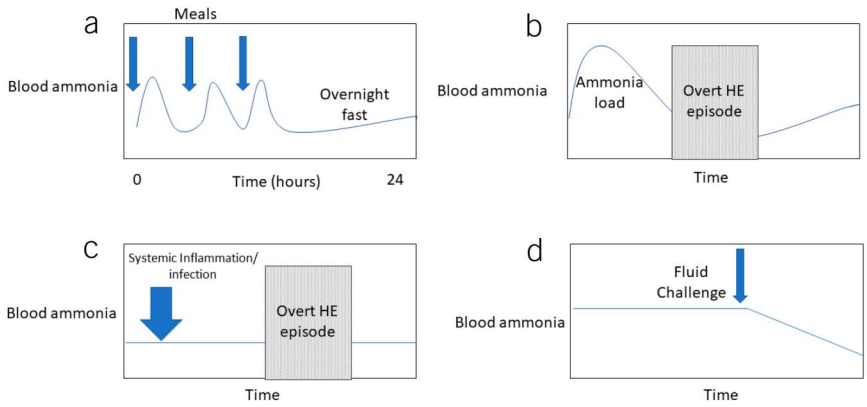

Figure 2. The variability and impact of common clinical scenarios on blood ammonia levels in a patient with compensated cirrhosis. (**a**) Blood ammonia levels will fluctuate throughout a 24-hour period. Typically, like the blood glucose, they rise following a protein rich meal and fall during the fasted state. Prolonged fasting leads to muscle breakdown and a paradoxical rise in blood ammonia. (**b**) Following an ammonia load, such as following an upper gastrointestinal bleed, ammonia rises. It is common, however, for the ammonia level to be already coming down when the patient presents with symptoms of overt encephalopathy; thus, a blood ammonia level may not be helpful at this point. (**c**) Systemic inflammation and infection act synergistically with ammonia to induce encephalopathy and may precipitate an episode in the absence of an ammonia rise. (**d**) A fluid challenge such as 1 L of crystalloid increases urinary ammonia excretion and lowers blood ammonia.

Table 2. Prominent minimal/covert hepatic encephalopathy cross-sectional norm-based validation studies

Author, year and country	Populations	Test(s)	MHE%	Validation results
Weissenborn et al. (123), 2001 Germany	Healthy controls n = 120 IBD = 24	PHES ≤ −5	25%	With a cutoff value set at −4 SD, PHES could discriminate MHE and G1HE from controls
Romero-Gomez et al. (124), 2007 Spain	Healthy controls n = 757 (PHES) n = 103 (CFF) Cirrhosis n = 114	PHES ≤ −5 CFF	31% 42%	PHES testing performance affected by age and education CFF weakly affected by Child-Turcotte-Pugh
Amodio et al. (125), 2008 Italy	Healthy controls n = 228 Cirrhosis n = 100	PHES ≤ −4 EEG	25% 31%	PHES testing performance affected by age and education
Dhiman et al. (126), 2010 India	Healthy controls n = 83 (age/sex matched) Cirrhosis n = 100	PHES ≤ −5 CFF < −2 SD (age-adjusted z score)	48% 21%	PHES testing performance affected by age and education (capped at 15) CFF affected only by age Grade 1 HE not included
Duarte-Rojo et al. (127), 2011 Mexico	Healthy controls n = 743 Cirrhosis n = 104	PHES ≤ −5	15%	PHES testing performance affected by age, education, occupation, and sex. Grade 1 HE performed as MHE
Allampati et al. (54), 2016 United States	Healthy controls n = 308 Cirrhosis n = 437	PHES ≤ −4 ICT < 0 EncephalApp < 0 (all adjusted scores)	27% 35% 54%	PHES, ICT, and EncephalApp performance affected by age, sex, and education
Campagna et al. (53), 2017 Italy	Healthy controls n = 208 IBD controls n = 40 Cirrhosis n = 327	PHES ≤ −4 (reference) S-ANT$_1$ ≤ 15 EEG	31%	ANT testing performance affected by age and education Grade 1 HE performed worse than MHE and better than Grade 2 HE

ANT, animal naming test; CFF, critical flicker frequency; CHE, covert hepatic encephalopathy; EEG, electroencephalogram; IBD, inflammatory bowel disease; ICT, inhibitory control test; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; S-ANT, Simplified Animal Naming Test.

Inadvertently, the wide range and dissimilarity of available neuropsychological tests and diagnostic cutoffs have created confusion and transformed MHE/CHE into uncharted territory for most clinicians (52). Simple and pragmatic testing recommendations are needed to make the evaluation of MHE/CHE more appealing to clinicians, further expand the field, and facilitate clinical trials leading to effective treatment. Engaging in some form of validated, routine testing is encouraged by the ISHEN. The use of a single, sensitive, and locally well-validated test, able to predict clinical outcomes, will suffice to diagnose MHE/CHE. Currently, screening for MHE/CHE has been restricted to targeted populations where this diagnosis and its potential therapy could benefit the most. These are people whose fitness to work or drive is questioned or those who have specific symptoms. The availability of point-of-care tests such as the animal naming test and EncephalApp Stroop allows for MHE/CHE to be evaluated at the bedside and in the outpatient clinic, potentially expanding the pool of screening candidates (53,54). Additional studies are indicated to validate diagnostic cutoffs in multiple centers and refine cutoffs for clinical and PRO prediction. Although establishing MHE/CHE diagnosis with 2 concomitantly abnormal tests has been advocated, this practice would result in a decreased prevalence of MHE/CHE without necessarily improving the accuracy of OHE prediction, given that each neuropsychological/neurophysiological test focuses on a particular cognitive/physiological set of skills/traits, and thus, divergent results are frequent (55–57). Finally, as with OHE, systemic cofactors affecting cognition (e.g., psychoactive medications, hyponatremia, and uncontrolled comorbid conditions) and neurological/psychiatric disorders (e.g., dementia and depression) need to be taken into account or ruled out in each patient with HE (56,58).

Consensus statements

1. Diagnosis of MHE/CHE should be based on a patient's performance on neuropsychological tests that are nationally and culturally validated, following availability and local expertise.
2. The combination of 2 or more tests to establish the diagnosis of MHE/CHE is discouraged. Although such practice would theoretically improve diagnostic accuracy, there is no clinical rationale or available evidence to substantiate it, and it

Table 3. Prominent minimal/covert hepatic encephalopathy longitudinal, outcome-based validation studies

Author, year and country	Population/exposure	Tests	End point	MHE/CHE	Outcomes and follow-up	Validation results
Dhiman et al. (126), 2010 India	n = 100 MHE	PHES ≤ −5 CFF Z score < 2	Survival	PHES 48% CFF 21%	Death 31% L2FU: 6% Approximately 2 yr	PHES ≤ −6 is an independent predictor of poor prognosis Abnormal CFF did not have any prognostic value on survival
Taneja et al. (128), 2012 India	n = 102 MHE	PHES ≤ −5 ICT ≥ 14 lures	OHE Survival	PHES 40% ICT 52%	OHE 12% Death 10% 6 m (average)	PHES independently predicted an increased risk of death and OHE ICT did not predict OHE or survival
Montagnese et al. (129), 2014 Italy	n = 132 CHE	PHES ≤ −24 CFF < 38/39 EEG	OHE ≥ 2	PHES 33% CFF 21–31% EEG 42%	OHE 22% Death 13% LT 13% 11 ± 7 m (available in 79 patients)	CHE by PHES or EEG predicted OHE CFF did not predict OHE
Riggio et al. (130), 2015 Italy	n = 216 MHE	PHES ≤ −4	OHE ≥ 2	PHES 44%	OHE 32% Death 26% L2FU 2% LT 7% 15 ± 12 m	MHE by PHES predicted OHE (with or without prior OHE)
Lauridsen et al. (57), 2015 Denmark	n = 129 MHE	PHES < −4 CRT < 1.9	OHE	PHES 34% CRT 53%	OHE 19% Death 23% 11 ± 6 m	MHE by PHES or CRT predicted OHE MHE by PHES and CRT predicted death
Ampuero et al. (131), 2015 Spain	n = 117 MHE	PHES < −4 CFF < 39	OHE Survival	PHES 26% CFF 37%	OHE 31% Death 21% 60 ± 34 m	MHE by CFF predicted death MHE by CFF predicted OHE
Thomsen et al. (132), 2016 UK	n = 106 CHE	PHES < −4 CFF < 39 EEG	OHE ≥ 2	PHES 60% CFF 54% EEG 42%	OHE 12% Death 12% L2FU 8% 8 ± 8 m	CHE by PHES did not predict OHE CHE by PHES and EEG predicted death
Allampati et al. (54), 2016 United States	n = 437 MHE	PHES ≤ −4 ICT Norms StE Norms	OHE ≥ 2	PHES 37% ICT 35% StE 54%	OHE 13% 11 (8–15) m	MHE by PHES, ICT, or StE predicted OHE (with or without prior OHE)
Campagna et al. (53), 2017 Italy	n = 202 HE < grade II (MHE/CHE)	PHES ≤ −4 S-ANT$_1$ EEG	OHE ≥ 2 Survival	PHES 23% ANT$_1$ 14% EEG 42%	OHE 39% Death 23% 12 m	ANT$_1$ predicted 1-yr risk of OHE and death
Ampuero et al. (133), 2017 Spain	n = 320 MHE	PHES < −4 CFF ≤39	Cirrhosis progression	PHES 31% CFF 43%	Cirrhosis progression 38% Death 19% LT 11% 3.5 ± 1.8 y	MHE linked to cirrhosis progression (65% in MHE vs 32% non-MHE)

ANT, animal naming test; CFF, critical flicker frequency; CHE, covert hepatic encephalopathy; CRT, continuous reaction time; EEG, electroencephalogram; ICT, inhibitory control test; L2FU, lost to follow-up; LT, liver transplantation; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; S-ANT, Simplified Animal Naming Test; StE, Stroop EncephalApp.

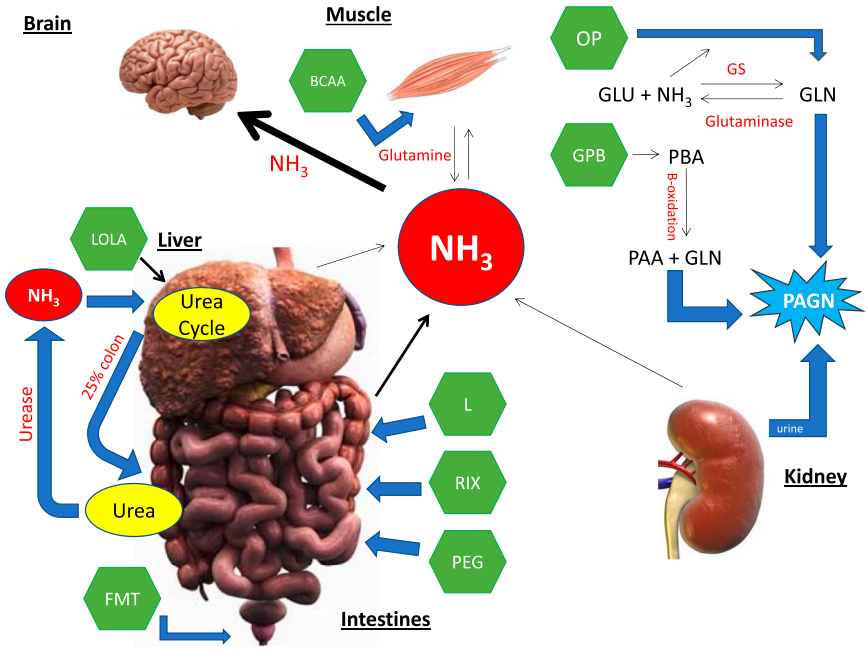

Figure 3. Targets for therapy in HE: NH3 circles represent circulating ammonia; NH3 squares represent glutamine-derived ammonia. FMT, fecal microbiota transplant; GLN, glutamine; GLU, glutamate; GNase, glutaminase; GS, glutamine synthetase; L, lactulose; NH3, ammonia; OP, ornithine phenylacetate; PAA, phenylacetic acid; GPB, glycerol phenylbutyrate; PAGN, phenylacetylglutamine; PBA, phenylbutyric acid; PEG, polyethylene glycol; RIX, rifaximin.

unnecessarily decreases the prevalence of the disease without improving its predictive usefulness.

3. Screening for MHE/CHE could ideally be offered to all patients with cirrhosis, but until point-of-care tests with widespread validation and links to outcomes are available, MHE screening can be restricted to targeted populations where fitness to work or drive is questioned or when prompted by specific symptoms.
4. Neuropsychological tests, such as psychometric hepatic encephalopathy score, critical flicker frequency, continuous reaction time, EncephalApp, and animal naming test have had validation and could be recommended for investigating MHE/CHE among patients with cirrhosis.

THERAPEUTIC OPTIONS

Current therapies

Current HE treatment (Table 3 and Figures 3 and 4) is based primarily on nonabsorbable disaccharides (lactulose and lactitol) and nonabsorbable antibiotics (rifaximin), and sometimes branched-chain amino acids (BCAAs), probiotics, and L-ornithine-L-aspartate (LOLA).

The nonabsorbable disaccharides are metabolized by colonic microbiota into short chain fatty acids, prohibiting growth of pathogenic ammonia-producing bacteria while facilitating the growth of potentially beneficial microbiota (59) (Table 4). The acidic environment facilitates conversion of ammonia (NH_3) to

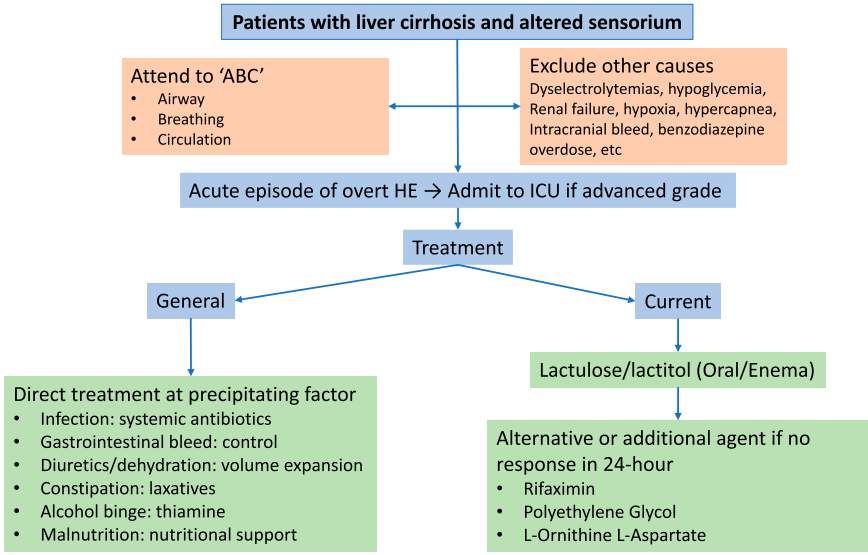

Figure 4. Algorithm for the management of a bout of overt hepatic encephalopathy.

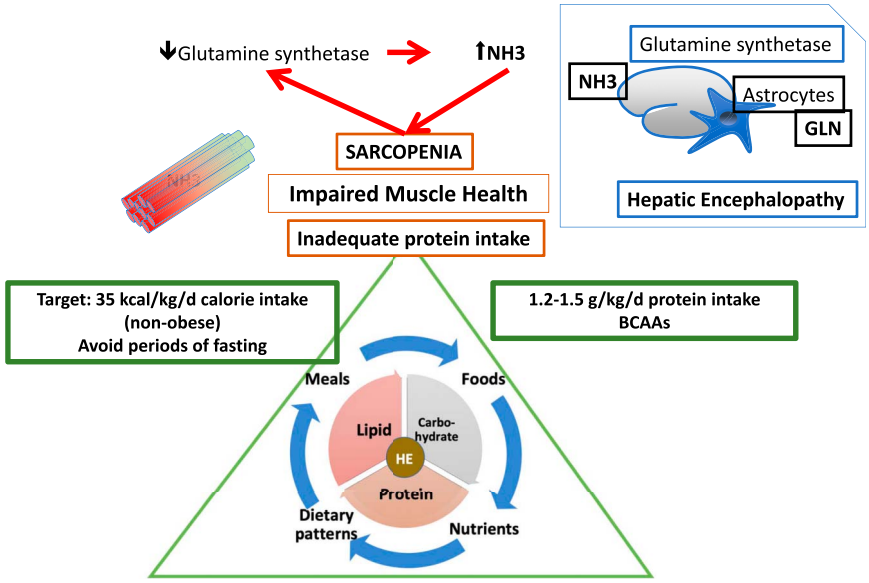

Figure 5. Nutrition in hepatic encephalopathy pivots on geometry of nutrition balancing nutrients and meals together with preserving calories and protein intake to avoid sarcopenia. A key factor on ammonia detoxification by glutamine synthetase pathway.

ammonium (NH_4), preventing the crossing of NH_3 through the blood-brain barrier, in addition causing a laxative effect resulting in removal of nitrogen-containing substances. A recent systematic review and network meta-analysis demonstrated that lactulose was the only agent effective in reversing MHE, preventing the development of OHE, reducing ammonia, and improving quality of life in MHE, but with tolerable adverse effects (60,61). An updated Cochrane review evaluating 38 trials (62) demonstrated a beneficial effect of lactulose on HE (relative risk [RR]: 0.58, 95% confidence interval [CI]: 0.50–0.69), cognition/MHE/CHE with a number needed to treat = 4, and associated mortality (RR: 0.59, 95% CI: 0.40–0.87) when compared with placebo/no intervention. With regard to recurrent HE admission, up to 22% of 30-day readmissions could have been prevented if patients were given instructions on titratable use of lactulose (63). Recurrent HE is seen in 47–57% at 1 year and is associated with poor prognosis. In a study, 125 patients who had recovered from a recent episode of HE were randomized to receive either lactulose or no lactulose for 20 months, and a higher proportion in the placebo group compared with patients receiving lactulose developed recurrence (64). Lactulose has also been shown to be effective in prevention of HE in patients with cirrhosis and acute variceal bleed (65).

The second major form of HE therapy is the nonabsorbable antibiotics (i.e., rifaximin), which alter intestinal microbiota. Others, including neomycin, vancomycin, and metronidazole, have limited long-term results and potential harmful side effects (26). In a landmark study, 299 patients with ≥2 episodes of OHE within 6 months were randomized to receive rifaximin or placebo (66). Overall, rifaximin significantly decreased the risk of developing HE breakthrough, with 22.1% events occurring in the rifaximin group vs 45.9% in the placebo group (HR with rifaximin, 0.42; 95% CI: 0.28–0.64; $P < 0.001$). Rifaximin also decreased the risk of hospitalizations (13.6%) vs placebo (22.6%, $P = 0.01$). The current recommendation is the use of rifaximin in addition to lactulose for the prevention of HE after a second OHE episode (26). Combination of lactulose and rifaximin is more effective in terms of complete reversal rather than lactulose alone in the treatment of OHE (67). In patients with corrected and limited precipitating factors, there is a weak recommendation to consider withdrawing these medications in the American Association for the Study of Liver Diseases (AASLD)/European Association for the Study of the Liver (EASL) guidelines.

Regarding probiotics compared with placebo/no intervention, VSL#3 was found to improve recovery (RR: 0.67, 95% CI: 0.56–0.79) and reduce the development of OHE (RR: 0.29, 95% CI: 0.16–0.51), with no impact on mortality (RR: 0.58, 95% CI: 0.23–1.44) (68). Although VSL#3 has not been FDA approved for all uses, it can be prescribed, however insurance companies might not cover the costs, because it is considered a probiotic medical food.

BCAAs are metabolized by skeletal muscle, and in cirrhosis, plasma concentrations of BCAAs and zinc are decreased. There are convincing data regarding the use of oral BCAAs in preventing HE recurrence from 4 studies (69–72) and 2 studies with leucine-enriched supplementation alone (73,74). A recent Cochrane review comprising 827 patients comparing BCAA with no intervention, placebo, neomycin, diet, or lactulose showed that BCAAs had a beneficial effect on HE with a number needed to treat of 5 (RR: 0.73, 95% CI: 0.61–0.88) (75). Excluding studies with a lactulose or neomycin control in a sensitivity analysis, BCAAs had a beneficial effect on HE (RR: 0.76, 95% CI: 0.63–0.92), with no difference between BCAAs and lactulose or neomycin (RR: 0.66, 95% CI: 0.34–1.30) and no effect on quality of life and mortality. Oral BCAAs can be used as an alternative or additional agent to treat patients with refractory HE (26); however, costs and palatability might be problematic.

Although zinc is a cofactor for enzymes of the urea cycle, zinc deficiency can be seen very commonly in patients with cirrhosis. One recent meta-analysis suggested an improvement in psychometric tests (i.e., number connection test) with zinc supplementation, without any influence on HE recurrence (76). As treatment ensues per standard of care for an underlying HE episode, one might consider adding zinc supplementation if zinc deficiency is confirmed, although the reliability of assays for zinc has been called into question.

Table 4. Standard, additional, and newer medical therapies in the treatment of hepatic encephalopathy

Treatment	Mechanism of action
Standard therapy (medical and procedural)	
Nonabsorbable disaccharides (lactulose or lactitol)	Osmotic laxative, prebiotic, and gut-acidifying agent
Nonabsorbable antibiotics (rifaximin)	Alters gut microbiota structure and function
Embolization of large portosystemic shunts	Decreasing systemic ammonia shunting
Alternate/additional therapy	
Branched-chain amino acids	Reduce ammonia from circulation by its conversion to glutamine
L-ornithine-L-aspartate (LOLA)	Nitrogen removal in the form of glutamine in the gut and urine
Emerging therapy—clinical stage	
Polyethylene glycol (PEG) 3350-electrolyte solution	Purgative; causes water to be retained in the colon and produces a watery stool
Albumin administration/dialysis	Scavenge reactive oxygen species/removal of toxins
Ornithine phenylacetate	Nitrogen removal in the form of urinary phenylacetylglutamine
Glycerol phenylbutyrate	Nitrogen removal in the form of urinary phenylacetylglutamine
Fecal microbiota transplantation	Reversal of gut dysbiosis
Emerging therapy—preclinical stage	
Liposome-supported peritoneal dialysis (LSPD)	Peritoneal extraction of small ionizable molecules (e.g., ammonia or drugs) in to the scavenging vesicles
GABAA receptor modulating steroid antagonists (GAMSA)	3-beta-hydroxysteroid counteracts the effects of neurosteroids, which decreases GABA-ergic tone
Glutamine synthetase replacement	AM-535, a recombinant GS, reduced ammonia effectively in cirrhosis and urea cycle enzyme deficiency

In a recent meta-analysis of 10 randomized controlled trials and 884 patients, LOLA was noted to improve all grades of HE compared with placebo/no intervention (RR: 1.36, 95% CI: 1.10–1.69, $P = 0.005$) and decrease blood ammonia levels (77). This effect was noted with both oral and intravenous (IV) formulations. In patients nonresponsive to current therapies, IV LOLA can be used as an additional or alternate agent (26,78,79); however, LOLA is not currently available in the United States.

Emerging therapies—clinical stage

Polyethylene glycol. Off-label use of polyethylene glycol (PEG)-3350 electrolyte solution for OHE treatment was studied in the HELP trial and other trials. Patients in the PEG arm, most of whom had already received lactulose before enrollment, had a significant improvement in HE grades compared with lactulose, with a more rapid resolution of HE (80–82) (Table 3).

Albumin. It is a multifunctional protein synthesized in the liver; it has anti-inflammatory properties and binds and clears many toxic substances, which accumulate in liver failure. Combination of lactulose with albumin has been demonstrated to be more effective than lactulose alone in complete reversal of HE (83). The binding properties of albumin have been the basis for the development of extracorporeal liver assist devices. In addition, the ANSWER trial also showed that albumin reduced development of grade 3–4 HE (incidence rate ratio 0.48 [0.37–0.63]) (84).

Ornithine phenylacetate. The combination of ornithine and phenylacetate increases hepatic and muscle ammonia detoxification via the stimulation of the enzyme glutamine synthetase (GS) mainly in the skeletal muscles. The resulting production of glutamine is converted to phenylacetylglutamine which can not be metabolized by glutaminase in the gut and is excreted in the urine. LOLA also detoxifies ammonia by the conversion of L-ornithine to glutamine in the muscle, which is readily converted back into glutamate and ammonia by glutaminase present in the gut (85) Ornithine phenylacetate significantly lowers blood ammonia in different animal models of liver disease/failure; the results of a phase 2b study demonstrated that it reduces ammonia concentration in patients with OHE in a dose-dependent manner, although the study failed to meet its primary end point (86).

Glycerol phenylbutyrate. In a randomized, double-blind, controlled study, glycerol phenylbutyrate was demonstrated to lower ammonia and significantly reduced the proportion of patients who experienced an HE event and was associated with fewer HE hospitalizations (87).

Fecal microbiota transplantation. Fecal microbiota transplantation from healthy donors improves gut dysbiosis in patients with cirrhosis. One case report, 1 case series, and 2 randomized clinical trials using enema or capsules have demonstrated safety, improved dysbiosis, and encouraging trends toward improving clinical outcomes (88–92). Larger studies are underway to assess further safety and efficacy.

Emerging therapies—preclinical stage

Liposome-supported peritoneal dialysis. Weak bases, including drugs or ammonia, diffuse from the blood to the peritoneal space and into the acidic interior of the transmembrane pH gradient liposomes (Table 3). They become protonated (DH+ and NH4+, respectively) in the liposome's aqueous core and become trapped in the core because the diffusion of the protonated species through the phospholipid membrane is hindered. These

liposomes can be removed during peritoneal dialysis. In a rat model of cirrhosis, liposome-supported peritoneal dialysis removed large amounts of plasma ammonia resulting in attenuation of cerebral edema compared with conventional peritoneal dialysis (93), but is unclear whether this could work in the absence of ascites.

GABA-A receptor modulating steroid antagonists. Patients with HE have increased GABA-ergic tone (neuroinhibitory), which is potentiated by neurosteroids. 3-beta-hydroxysteroid has been demonstrated to effectively antagonize this mechanism and restore brain functions in rats with experimental hyperammonemia and HE (94,95).

GS replacement. Glutamine is an intermediate in ammonia metabolism, especially in the urea cycle is deficient as in patients with liver disease and in patients with urea cycle abnormalities. Preliminary data from a study demonstrated that AM-535, a recombinant GS, reduces ammonia effectively in an animal model of cirrhosis and urea cycle enzyme deficiency (96).

TIPS AND HE

TIPS has been used for the treatment of the complications of portal hypertension, such as variceal bleeding and refractory ascites and hepatic hydrothorax. However, emergence of HE after this procedure is of major concern, and the incidence ranges between 19% and 32%. Both diversion of portal blood from the liver due to portacaval shunting and decreased liver metabolic capacity are related to post-TIPS HE (97).

Although most of the episodes of post-TIPS HE are usually related to precipitating events, a small number of patients with cirrhosis experience persistent HE, refractory to standard medical treatment. Although the former may be treated with a standard approach to treat OHE, the latter would require a reduction in the size of shunt or shunt occlusion, which may also serve as a bridge to liver transplantation (98).

There are no proven prophylactic treatments for post-TIPS HE that have been fully published. A recent study by Wang et al. (99) demonstrated that TIPS with 8 mm instead of 10-mm covered stents halved the risk of spontaneous OHE and reduced hepatic impairment while having the similar stent function. Pharmacological prophylaxis with lactitol or rifaximin for post-TIPS HE was not effective in preventing the episodes of HE (100); however, their combination has never been formally tested. In patients who received TIPS, Bureau et al. (101) demonstrated that the use of preventive rifaximin (600 mg twice daily) was associated with a lower risk of HE and a higher rate of transplant free survival during the post-TIPS 6-month period of treatment.

Although treatment with lactulose ± rifaximin are the main prophylactic treatment regimens for HE, some suggest considering withdrawing therapy in a select subgroup of HE patients if precipitants can be controlled (i.e., recurrent infections, variceal bleeding, nutritional status, and liver function). Although the evidence for this is uncertain, future research is required to make final conclusions in this specific area.

CENTRAL-ACTING MEDICATION THERAPY

As anxiety, depression, and pain symptoms become more prevalent worldwide, medications such as opioids and benzodiazepine have been prescribed at increasingly higher rates. Health care providers should be cautious when considering the use of these medications in the cirrhotic population because long-term use of these agents can contribute to cognitive impairment. Sedation for endoscopy does not impact cognitive function in a lasting manner in cirrhosis. In situations where narcotic or benzodiazepine overuse may be a factor in the confusion episode, naloxone or flumazenil treatment should be given to reverse narcotic or benzodiazepine toxicity/overdose and to confirm diagnosis. Centrally acting nonselective beta-blockers have been associated with an increased risk for incidental HE, and caution should be exercised when prescribing them to patients with decompensated cirrhosis (102).

Consensus statements

CHE/MHE therapy

1. Once CHE/MHE is diagnosed, these patients are prone to develop OHE; hence, therapy can be considered on a case-by-case basis.
2. Lactulose could be recommended for treating MHE as a trial run in those whom testing is positive.

OHE acute episode

1. Identify and treat precipitating factors for HE.
2. Lactulose is the first choice for treatment of OHE by enema or oral route based on severity of HE. Lactulose is recommended for secondary prophylaxis after the first episode
3. IV LOLA can be used as an alternative or additional agent to treat patients nonresponsive to lactulose.
4. PEG can also be used in case of ileus or prior intolerance to lactulose or based on local preference

Prevention of recurrence

1. Lactulose is recommended for prevention of recurrence of OHE episode(s) after the initial episode.
2. Rifaximin is recommended as an add-on to lactulose for prevention of recurrent episodes of OHE after the second episode

NUTRITIONAL ISSUES AND PROs

Nutrition and HE

Malnutrition, sarcopenia, frailty, and HE are interwoven conditions connected in part by impaired muscle health. Muscle acts as a nonhepatic source of ammonia disposal via glutamine synthesis (103,104). Sarcopenia has therefore been associated with higher rates of HE including those undergoing TIPS (105,106). Hyperammonemia itself contributes to sarcopenia by direct muscle toxicity and by upregulation of myostatin, which in turn impairs protein synthesis and increases autophagy (107,108). Muscle breakdown is further precipitated by inadequate nutritional intake. Recognized as a state of accelerated starvation, cirrhosis is associated with hepatic glycogen depletion and a rapid shift to protein catabolism and muscle breakdown to maintain gluconeogenesis (104) (Figure 5).

Considering the above, all patients with cirrhosis and, in particular, those with HE should receive adequate HE therapy and personalized nutritional counseling around (i) guideline-based target calorie intake (targets have varied across guidelines, but the latest EASL consensus recommends at least 35 kcal/kg body weight per day in the nonobese and dietician-guided intake in the obese), (ii) adequate protein intake (1.2–1.5 g/kg body weight per day), (iii) the need to avoid periods of fasting (avoiding fasting for longer than 3–4 hours, with focus given to

a late evening and early morning protein- and carbohydrate-containing meal/snack), and (iv) in patients with ascites, sodium restriction to 2 g/d with recognition that this may need to be liberalized if it significantly compromises the palatability of food (108–110) (Figure 1). In the randomized controlled trial by Cordoba et al., (111) protein restriction was found to be detrimental in hospitalized patients with HE, demonstrating no change in HE resolution but inducing protein catabolism as measured using the glycine-N15 infusion method. A late evening snack has been associated with improved nitrogen balance, increased muscle mass, improved quality of life, and reduced HE (112–114). Moreover, a randomized trial of guideline-based calorie and protein intervention for 6 months has demonstrated improvements in neurocognitive testing and reductions in OHE (115). An inpatient study showed that nutritional consultation was associated with reduced readmissions (116). From a practical standpoint, patients should be advised to balance intake of fat, carbohydrate, and protein following the geometry of nutrition concept (117). Protein could be obtained from multiple sources (meal supplements, protein powder, meat, dairy, and vegetable proteins [e.g., beans and tofu] (118)) to reduce food boredom and avoid the substitution by carbohydrate or fat. There is weak evidence to support an advantage of nonmeat (dairy/plant) proteins in cirrhosis (108,119,120). Additional studies are required to evaluate the impact of nutritional interventions on other clinically relevant outcomes including survival and hospitalization.

PROs

PROs have a major impact on health-related quality of life and clinical and psychosocial abilities. Classically, PROs from patients with cirrhosis are characterized by impairment in quality of life, worsening mental health, limited coping, and an increase in intrafamilial conflicts with overexertion by caregivers. Recognizing the profound impact these PROs can have, they should ideally be evaluated at diagnosis and repeated over time (45). Tools that could be included are health-related quality of life: Sickness Impact Profile (SIP) and Short Form 12 (SF-12)/Short Form 36 (SF-36) score, including sleep disorders (Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale); mental health: Beck-II Depression and Anxiety Inventory; coping strategies: COPE-28; self-reported efficiency scale; dimensional scale of self-perceived social support; and intrafamilial relationship by scale of social climate intrafamilial and perceived caregiver burden. Acknowledging and addressing PROs, mainly from a psychological point of view, is essential to improving quality of life in both patients and caregivers. Mindfulness and support group therapy may also be useful (121,122) as may the early involvement of palliative care, providing respite options for caregivers and making caregivers aware of the support lines and online materials available from their local liver foundations.

Consensus statements

1. In patients with cirrhosis and HE, BCAA supplementation should be considered for the prevention of HE recurrence, especially if dietary protein intake is inadequate.
2. Clinical teams should aim toward providing personalized and practical dietary counseling around how to achieve guideline-based calorie targets, protein targets, and eat frequent meals and snacks to avoid prolonged periods of fasting for all patients with cirrhosis and HE.
3. Protein restriction should be avoided in patients with HE.
4. HE has a profound impact on both patients and caregivers.
5. Efforts should be made to elicit patient-reported and caregiver-reported outcomes at diagnosis and intermittently over time to determine when optimization of therapy or additional supports may be required.

CONFLICTS OF INTEREST

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APPENDIX

The review mentioned a probiotic VSL#3, which is now known by the "De Simone Formulation." To the best of our knowledge, there are no randomized trials that have assessed the current product known as VSL#3 in hepatic encephalopathy. The current product known as VSL#3 is not the same formulation as the original product invented by Professor De Simone.

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