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Current approach to treatment of minimal hepatic encephalopathy in patients with liver cirrhosis

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Abstract

Minimal hepatic encephalopathy (MHE) corresponds to the earliest stage of hepatic encephalopathy (HE). MHE does not present clinically detectable neurological-psychiatric abnormalities but is characterized by imperceptible neurocognitive alterations detected during routine clinical examination *via* neuropsychological or psychometrical tests. MHE may affect daily activities and reduce job performance and quality of life. MHE can increase the risk of accidents and may develop into overt encephalopathy, worsening the prognosis of patients with liver cirrhosis. Despite a lack of consensus on the therapeutic indication, interest in finding novel strategies for prevention or reversion has led to numerous clinical trials; their results are the main objective of this review. Many studies address the treatment of MHE, which is mainly based on the strategies and previous management of overt HE. Current alternatives for the management of MHE include measures to maintain nutritional status while avoiding sarcopenia, and manipulation of intestinal microbiota with non-absorbable disaccharides such as lactulose, antibiotics such as rifaximin, and administration of different probiotics. This review analyzes the results of clinical studies that evaluated the effects of different treatments for MHE.

Key Words: Minimal hepatic encephalopathy; Sarcopenia; Probiotics; Non-absorbable disaccharides, Rifaximin; L-ornithine-L-aspartate

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Core Tip: Minimal hepatic encephalopathy (MHE) is a frequent complication in patients with liver cirrhosis. MHE affects the quality of life and increases the risk of falls and car accidents, worsening patients' prognoses; however, there is no standard of care. Current alternatives for the management of MHE include measures to maintain the nutritional status while avoiding sarcopenia, manipulation of intestinal microbiota with non-absorbable disaccharides such as lactulose, antibiotics such as rifaximin, and administration of different probiotics. This review analyzes the results of clinical studies that evaluated the effects of different treatments for MHE.

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INTRODUCTION

Minimal hepatic encephalopathy (MHE) corresponds to the earliest stage of hepatic encephalopathy (HE) (Table 1) and is characterized by imperceptible neurocognitive alterations detected during routine clinical examination through neuropsychological or psychometrical tests[1-3]. The prevalence of MHE in patients with liver cirrhosis varies from 23.7% to 56.6%, depending on the diagnostic criteria and studied population[4-8]. MHE predisposes patients to the development of overt HE (OHE)[9-11]; it has been reported that 50% of patients with MHE develop OHE within 3 years [12]. MHE may also affect daily activities, negatively reduce job performance and quality of life (QOL), and increase the risk of causing car accidents[6,13,14].

ASSESSMENT OF MHE

Despite the existence of several grading instruments that allow for the distinction of patients with MHE among those without neurocognitive alterations, there are no specific tests that discriminate the different grades of covert HE (CHE). Table 2 shows some of the tools used for the diagnosis of MHE. Although formal neuropsychological assessment is the best method to identify neurocognitive deficits, there is no standard battery for MHE recognition, so neuropsychologists must interpret and assess these tests. Therefore, other neuropsychological, computerized, and short neuropsychological batteries have been suggested for its identification[15-17].

Even when surveillance of MHE is possible in every patient with liver cirrhosis, a screening that enables us to distinguish patients at risk of suffering from or causing car accidents among active drivers or distinguish patients manifesting cognitive deterioration or noticeable low job performance has been suggested[15].

ASSOCIATED CLINICAL CONDITIONS

Certain conditions that have been addressed as contributors to the development of MHE and are therefore considered potential therapeutic targets. They are as follows.

Hyperammonaemia

The increase in arterial ammonia has been found in patients manifesting some signs of cerebral dysfunction such as mild lethargy, brisk deep tendon reflexes, or increased resistance to passive arm movement[18], and in patients with the specific diagnosis of MHE[19-23] including those with concomitant MHE and sarcopenia[7,23]. An increase in the production of ammonia may be related to dysbiosis, small intestinal bacterial overgrowth (SIBO), or *Helicobacter pylori* infection as a result of increased activity of bacterial urease, intestinal urea hydrolysis, and absorption of nitrogenous products[20, 24]. This, together with decreased intestinal motility and altered integrity of the intestinal barrier, facilitate the increase in bacterial translocation and endotoxin release

Table 1 Classification of the different stages of hepatic encephalopathy

Diagnostic criteria	Classification stages					
	Unimpaired	Covert hepatic encephalopathy		Overt hepatic encephalopathy		
ISHEN		MHE	Grade I	Grade II	Grade III	Grade IV
WHC	No encephalopathy, no history of OHE	Imperceptible cognitive alterations during routine clinical examination	Trivial lack of awareness; Euphoria or anxiety; Shortened attention span; Impairment of addition or subtraction; Altered sleep rhythm	Lethargy or apathy; Disorientation for time; Obvious personality change; Inappropriate behavior; Dyspraxia asterixis	Somnolence to semistupor; Responsive to stimuli; Confused; Gross disorientation; Bizarre behavior	Coma

ISHEN: International Society for Hepatic Encephalopathy and Nitrogen Metabolism; MHE: Minimal hepatic encephalopathy; OHE: Overt hepatic encephalopathy; WHC: West Haven Criteria.

Table 2 Diagnostic tools for the diagnosis of minimal hepatic encephalopathy

Test type	Test approach to differentiate MHE from unimpaired subjects
Formal neuropsychological; Assessment	No standard battery for MHE has been designed, but could include test of attention, executive function, psychomotor ability, and speed information processing to evaluate cognition, and mental activity.
Neuropsychological	EEG: Detect changes in cortical cerebral activity; Evoked potentials: Measurement of firing patterns of single cells or cell clusters.
Computerised	SCAN test: Measures speed and accuracy to perform a digit recognition memory task of increasing complexity; CFF: Degree of vigilance; CRT: Relies on the repeated registration of the motor reaction time to auditory stimuli. Measures the stability of the reaction time; Stroop test: Evaluates psychomotor speed and cognitive flexibility; ICT: Test of response inhibition and working memory.
Imaging	MRI: Through mean kurtosis values, evaluates six regions of interest, and amplitude of low frequency fluctuation values, which correlate with PHES values.
Short neuropsychological batteries	PHES: Evaluates cognitive/psychomotor processing speed and visuomotor coordination (NCT-A, NCT-B, SDT, LTT, DST); ANT: Cognitive function related to prefrontal anterior/cortex cortical areas.

ANT: Animal naming test; CFF: Critical flicker frequency; CRT: Continuous reaction time; DST: Digit symbol test; EEG: Electroencephalogram; ICT: Inhibitory control test; LTT: Line tracing test; MHE: Minimal hepatic encephalopathy; MRI: Magnetic resonance imaging; NCT-A: Number connection test A; NCT-B: Number connection test B; PHES: Psychometric hepatic encephalopathy score; SDT: Serial dotting test.

to the circulation[25,26].

Sarcopenia

A low skeletal muscle index (SMI) is found in 58% of patients with liver cirrhosis; however, its prevalence increases to 84% in patients with MHE compared to patients without MHE, of which 17-30% are sarcopenic[7,21,23]. In all, 41% to 49% of patients with MHE show muscle depletion according to a mid-arm muscle circumference (MAMC) and triceps skinfold thickness (TSF) below the 5th percentile and a decreased muscle function[7,21]. Protein malnutrition is associated with MHE; 49% of these patients are undernourished compared to 28-30% of patients without cognitive alterations[7].

SIBO

The concurrence of SIBO is greater in patients with MHE (38.6-65.4%) than in those without neurocognitive deterioration (8.8%-16.13%)[22,25-27].

Dysbiosis

An association of specific bacterial species and HE has been suggested[28,29]. An increase in *Enterobacteriaceae* (*Escherichia coli*) and *Staphylococcus spp.* has been related to MHE, and nearly 22% of patients with cirrhosis and MHE have *H. pylori* infection[20,29].

Inflammatory factors

Interleukin 6 (IL-6), IL-17a, and IL-18 cytokine concentrations are increased in cirrhotic patients with alterations in the psychometric tests but with no clinical manifestations of HE[30-32].

Hyponatremia

In all, 31% of patients with MHE have hyponatremia compared to 16% of patients without neurocognitive alterations[7].

CLINICAL TRIALS FOR TREATMENT OF MHE

There has been a striking increase of studies addressing the treatment of MHE, which is mainly based on the strategies and previous management of OHE. Tables 3-5 evaluate strategies aimed toward achieving greater detoxification and lower production of ammonia.

STRATEGIES TO INCREASE THE DETOXIFICATION OF AMMONIA

Energy-protein intake

The rationale for increasing the caloric and protein intake for the treatment of MHE (30-45 kcal/kg/d and 1.2-1.5 g protein/kg/d, respectively) considers the association of the neurocognitive alterations and sarcopenia in patients with MHE, together with the enhancement of ammonia detoxification by preserving muscle mass and avoiding protein malnutrition[7,33-36]. Only in one of these studies was the protein intake set to provide 1.0-1.5 g/kg/d for the treatment of MHE; this protein was solely of vegetable origin[33].

In patients without previous HE, the reversion of MHE upon normoprotein diet implementation (1.0-1.5 g/kg of ideal body weight/d) was attested to in 57.8% of the patients after 4 wk of dietary treatment. The response rate further increased to 68.4% by week 8; however, neither dietary compliance nor other factors possibly related to the reversion such as amino acid supplementation or use of lactulose and/or antibiotics were assessed. Moreover, results were not compared against a control group[37].

Regarding the effect of ammonia concentration, a dietary intake of at least 1 g vegetable protein/kg/d and 30 kcal/kg/d reported an average change of -6.53 μmol ammonia/L *vs* the basal concentrations after 6 mo of treatment[33]. An average decrease of 20.8 μmol ammonia/L with respect to the basal concentration was achieved with the administration of branched-chain amino acids (0.25 g/kg/d) and a standardized diet (35 kcal/kg/d and 1 g of protein/kg/d); however, patients were also receiving lactulose at the time of the study[34]. These dietary modifications have also improved some of the sarcopenia indicators, such as TSF and handgrip values in patients with MHE receiving dietary counseling; this study does not report what these values were before the study was started[33].

In some studies, a starting diet is standardized according to the minimum energy and protein requirements before the implementation of a specific treatment; however, dietary compliance was not measured in any of the aforementioned studies (Tables 3-5).

L-ornithine-L-aspartate

This compound provides substrates to metabolic pathways involved in the detoxification of ammonia by stimulating both the urea synthesis and glutamine synthesis [38]. The administration of L-ornithine-L-aspartate (LOLA) improved MHE in 35% of the patients, 47% with lactulose, 35% with VSL#3 probiotic, and 10% with a placebo during a 3-mo treatment (Table 3)[39]. The administration of LOLA also showed a 11.42% improvement in the mean critical flicker frequency threshold (CFF) after 8 wk of treatment[40]. Ammonia decreased an average of 8.94% compared to the initial concentrations in patients who were treated with an infusion of LOLA for just 7 d; however, nausea was a side effect in 15% of the patients[41].

Table 3 Published studies using several options for minimal hepatic encephalopathy treatment: Diet, branched-chain amino acids or L-ornithine-L-aspartate supplementation, and probiotics/symbiotics

Ref.	Study type	Follow-up (wk)	MHE diagnosis	Active treatment (s)	Objectives	Patients (n)	Main results/impact measures
No history of OHE ¹							
Kato <i>et al</i> [37], 2012	Quasi-experimental	8	NCT-A, NCT-B, BDT, DST	30-35 Kcal + 1.0-1.5 g/kg of protein/d ^{3,4}	Reversal of MHE	19	11/19 (57.8%) recovered at 4 wk, and 13/19 (68.4%) at 8 wk ⁸
Maharshi <i>et al</i> [33], 2016	Randomized ²	24	NCT-A/FCT-A, NCT-B/FCT-B, DST, LTT, SDT	Nutritional education/no nutritional therapy ^{3,5}	Reversal of MHE	60/60	27/38 (71.1%) <i>vs</i> 8/35 (22.8%); 27/60 (45%) <i>vs</i> 8/60 (13.3%), when considering PPS and ITT analysis.
Malaguarnera <i>et al</i> [64], 2008	Randomized, double-blind	13	NCT-A, NCT-B, BDT, SDT, TMT, AVL, EGG	Acetyl-L-carnitine /placebo ⁵	Cognitive scores ⁷	60/55	Changes of mean values in at least 20.71% to 32.79% respect to basal values ⁸
Bajaj <i>et al</i> [34], 2014	Randomized, double-blind	8	NCT-A, NCT-B, DST/BDT	LGG/placebo	Psychometric scores ⁷	18/19	Improvement from 1.02% to 15.89% from baseline values
Bajaj <i>et al</i> [44], 2008	Randomized ²	8	NCT-A, BDT, DST	Probiotic yogurt/no treatment ^{4,5}	Reversal of MHE	17/8	ITT analysis: Reversal in 12/17 (70.58%) <i>vs</i> 0/7 (0%)
Mittal <i>et al</i> [39], 2011	Randomized ²	12	NCT-A/FCT-A, NCT-B/FCT-B, BDT, PC	Lactulose/VSL#3, LOLA/no treatment	Reversal of MHE	40/40/40/40	ITT analysis: Reversal of 4 (10%) in no treatment group, 19 (47.5%), 14 (35%) and 14 (35%)
Possible history of OHE ¹							
Egberts <i>et al</i> [35], 1985	Crossover, double blind	6	EGG, DST, MVT-B	BCAAs/placebo	Psychometry and EGG	11/11	Improvement in psychometric test from 0 to 13.63% respect to basal values in DST ⁸
Ndraha <i>et al</i> [36], 2011	Double blind, randomized	2	CFF	BCAAs + LOLA/BCAAs ⁴	CFF	17/17	Improvement in CFF 7.0% and 1.96% values (Hz), respect to baseline
Kircheis <i>et al</i> [41], 1997	Randomized, double-blind	1	NCT-A	LOLA infusion <i>vs</i> Placebo ⁵	Psychometry ⁷	26/27	Improvement in mean time to respond NCT-A from baseline (29% <i>vs</i> 9.73%)
Liu <i>et al</i> [29], 2004	Randomized ²	4	NCT, BAEP	Symbiotics + fermentable fibers/fermentable fibers/placebo ^{4,5}	Reversal of MHE ⁷	20/20/15	Reversal of 50% in symbiotic group, 50% in fermentable fibers group and 13% in placebo. Not statistically significant until compression of treatment groups <i>vs</i> placebo ($P = 0.03$) ⁹
Dhiman <i>et al</i> [65], 2014	Double blind, randomized	24	NCT-A/FCT-A, NCT-B, SDT, DST, LTT	VSL#3/placebo	Psychometric scores ⁷	16/13	Mean psychometric scores before and after probiotics -9.9 (-13.3 to -6.5) <i>vs</i> -5.7 (-8.4 to 2.9) $P = 0.014$. Proportion of patients with scores < -5 did not change in either group ¹⁰
Malaguarnera <i>et al</i> [45], 2007	Randomized, double-blind	17	TMT-A, TMT-B, BDT, MMSE	<i>Bifidobacterium longum</i> + FOS/placebo ⁵	Psychometry	30/30	No statistical or clinical change was found respect to basal values at, 30, 60, 90 and 120 d
Ziada <i>et al</i> [48], 2013	Randomized ²	4	NCT-A, DST, SDT	Lactulose/L, acidophilus/control ^{5,6}	Psychometry	24/26/25	Normalization of test occurred in 13/24 (54.2%), 14/26 (53.8%), and 3/25 (12%)

¹Studies in which the clinical history to the OHE events is specified or no is specified within the inclusion criteria.

²Unblinded study.

³The effect of other treatments for MHE was not studied.

⁴Treatment compliance was not assessed in one or different group of treatments.

⁵Diet was not standardized together with the suggested treatment.

⁶The treatment that the control group received was not specified.

⁷Secondary objectives within the study.

⁸The analysis was performed within the same group (before–after treatment) despite the study design.

⁹Addition of the effect of two maneuvers.

¹⁰MHE reversion was not measured. AVL: Auditory verbal learning test; BAEP: Brainstem auditory evoked potential; BCAAs: Branched-chain amino acids; BDT: Block design test; CFF: Critical flicker frequency; DST: Digit symbol test; EEG: Electroencephalogram; FCT-A: Figure connection test A; FCT-B: Figure connection test B; FOS: Fructooligosaccharides; ITT: Intention to treat; LOLA: L-ornithine-L-aspartate; LTT: Line tracing test; MHE: Minimal hepatic encephalopathy; MMSE: Mini mental state examination; MVT-B: Multiple choice vocabulary test B; NCT-A: Number connection test A; NCT-B: Number connection test B; PC: Picture completion; PPS: Per Protocol Analysis Set; SDT: Serial dotting test; TMT: Trail making test; TMT-A: Trail making test A; TMT-B: Trail making test B.

Table 4 Published studies using non-absorbable disaccharides for minimal hepatic encephalopathy treatment

Ref.	Study type	Follow-up (wk)	MHE diagnosis	Active treatment (s)	Objectives	Patients (n)	Main results/impact measures
No history of OHE ¹							
Prasad <i>et al</i> [47], 2007	Randomized ²	12	NCT-A/FCT-A, NCT-B/FCT-B, PCT, BDT	Lactulose <i>vs</i> no treatment	Psychometry	31/30	ITT analysis: Improvement in 20/31 (64.5%) <i>vs</i> 2/30 (6.7%); NNT:2
Horsmans <i>et al</i> [55], 1997	Randomized, double-blind	2	NCT, RIT.	Lactulose <i>vs</i> lactose as placebo ^{4,5}	Psychometry	7/7	Improvement in time on Psychometric test on lactulose group respect to basal values. ⁷ Rate of improvement NCT: 5/7 (71.42%) <i>vs</i> 1/7 (14.28%); NNT:2
Sharma <i>et al</i> [50], 2008	Randomized ²	4	NCT-A/FCT-A, NCT-B/FCT-B, P300ERP	Lactulose, probiotics, and lactulose + probiotics ⁵	Psychometry, P300ERP ⁶	35/35/35	Normalization in 17/31 (54.8%), 16/31 (51.6%), and 17/30 (56.6%) of MHE patients
Morgan <i>et al</i> [60], 1989	Cross-over, randomized	8 ³	EEG, NCT, DST, DCT	Lactulose <i>vs</i> lactitol ⁴	Psychometry	14/14	No differences between treatments in median change in psychometric time or scores
Possible history of OHE ¹							
Dhiman <i>et al</i> [51], 2000	Randomized ²	12	NCT-A/FCT-A, NCT-B/FCT-B, PCT, BDT.	Lactulose <i>vs</i> no lactulose ⁴	MHE improvement	14/12	Improvement in 8/10 (80.0%) <i>vs</i> 0/8 (0.0%), $P < 0.001$ ⁸
Wang <i>et al</i> [49], 2019	Randomized ²	8	NCT-A, DST	Lactulose <i>vs</i> no lactulose	MHE reversal	67/31	ITT analysis: 43/67 (64.2%) <i>vs</i> 7/31 (22.6%); NNT: 3PPS: 41/59 (69.5%) <i>vs</i> 6/28 (21.4%); NNT: 2

¹Studies in which the inclusion criteria comprise patients with clinical history to the overt hepatic encephalopathy events.

²Unblinded study.

³Washout period of 4–6 wk between treatments.

⁴Compliance to treatment was not measured in one or the different treatment groups.

⁵Diet was not standardized according to the suggested treatment.

⁶Secondary objectives within the study.

⁷Analysis was performed within the same group (before–after treatment) despite the experimental design.

⁸Minimal hepatic encephalopathy reversion not measured. BDT: Block design test; DCT: Digit copying test; DST: Digit symbol test; EEG: Electroencephalogram; FCT-A: Figure connection test A; FCT-B: Figure connection test B; ITT: Intention to treat; MHE: Minimal hepatic encephalopathy; NCT: Number connection test; NCT-A: Number connection test A; NCT-B: Number connection test B; NNT: Number needed to treat; OHE: Overt hepatic encephalopathy; PCT: Picture completion test; PPS: Per protocol analysis set; RIT: Race track test.

STRATEGIES TO REDUCE THE PRODUCTION OF AMMONIA

Fiber supplementation

Dietary fiber as a prebiotic is a non-digestible food component that has a positive effect

Table 5 Published studies using antibiotics for minimal hepatic encephalopathy treatment

Ref.	Study type	Follow-up (wk)	MHE diagnosis	Active treatment (s)	Objectives	Patients (n)	Main results/impact measures
No history of OHE ¹							
Ahluwalia <i>et al</i> [66], 2014	Quasi-experimental	8	NCT-A, NCT-B, DST, BDS, LTT, SDT, ICT	Rifaximin ⁴	fMRI, ICT, MRS ⁵	20	Changes in ICT, improvement of 12% respect to baseline, indicating a better cognition
Bajaj <i>et al</i> [61], 2013	Quasi-experimental	8	NCT-A, NCT-B, DST, BDT, LTT	Rifaximin ⁴	Psychometry ⁵	20	Improvement in NCT-A time (11.8%), NCT-B time (11.8%), DST raw score (9.1%), BDT raw score (0.0%), LTT time (20.7%), LTT errors (39.8%), SDT time (12.3%) from basal values
Bajaj <i>et al</i> [67], 2011	Randomized, single-blinded	8	NCT-A, DST, BDT, ICT	Rifaximin/placebo ⁴	Driving performance, psychometry scores	21/21	Decrease of 46.6% of total errors respect to baseline in rifaximin group ($P < 0.001$) ⁶ . Improvement in NCT-A 91% <i>vs</i> 61% (NNT: 4); NCT-B: 81% <i>vs</i> 33% (NNT: 2); and ICT lures: 76% <i>vs</i> 43% (NNT: 3) ⁷
Sidhu <i>et al</i> [59], 2015	Randomized, non-inferiority trial	12	NCT-A, FCT-A, DST, PCT, and BDT	Rifaximin/lactulose	Reversal of MHE	57/55	ITT analysis shows a reversal at 2 wk: lactulose 40.0% <i>vs</i> rifaximin 52.63% (NNT: 8). ITT analysis at 3 mo shows reversal in 69.1% and 73.7% of lactulose and rifaximin, (NNT: 22)
Goyal <i>et al</i> [62], 2017	Prospective cohort	24	NCT-A, FCT-A, DST, PCT, BDT	Previous intake of Rifaximin compared to lactulose ^{3,4}	Maintenance of remission for MHE	42/38	Still free of MHE: Rifaximin 42.8% <i>vs</i> lactulose 50.0% (NNT: 14)
Possible history of OHE ¹							
Agrawal <i>et al</i> [24], 2011	Quasi-experimental	1	NCT, FTC, LTT.	Clarithromycin, lansoprazole, tinidazole ^{3,4}	Psychometric scores ⁵	35	Improvement in 12.7%, 13.3%, and 18.7% respect to basal mean time in NCT, FCT and LTT, respectively
Zhang <i>et al</i> [27], 2015	Quasi-experimental	5	NCT-A, NCT-B, DST	Rifaximin 1 wk ^{3,4}	Reversal of MHE	26	After a week, reversal present in 11/26 (42.3%)
Sidhu <i>et al</i> [56], 2011	Double-blind, randomized	8	NCT-A/FCT-A, DST, PCT, BDT	Rifaximin/placebo	Reversal of MHE	49/45	Reversal at 2 wk: 57% <i>vs</i> 18% (NNT: 3) At 8 wk: Reversal of 75.5% <i>vs</i> 20% (NNT: 2)
Sharma <i>et al</i> [40], 2014	Randomized ²	8	NCT-A/FCT-A, DST and/ or CFF	LOLA/rifaximin/Probiotics/Placebo ⁴	Reversal of MHE ⁵	31/31/32/30	ITT analysis: Improvement in CFF values (Hz) from baseline in 11.42%, 6.5%, 8.68%, and 2.28%

¹Studies in which the inclusion criteria comprise patient with clinical history to the overt hepatic encephalopathy events.²Unblinded study.³Compliance to treatment was not measured in one or the different treatment groups.⁴Diet was not standardized according to the suggested treatment.⁵Secondary objectives within the study.⁶Analysis was performed within the same group (before–after treatment) despite the experimental design.

⁷Minimal hepatic encephalopathy reversion not measured. BDT: Block design test; CFF: Critical flicker frequency; DST: Digit symbol test; FCT: Figure connection test; FCT-A: Figure connection test A; ICT: Inhibitory Control Test; ITT: Intention to treat; LTT: Line tracing test; MHE: Minimal hepatic encephalopathy; NCT: Number connection test; NCT-A: Number connection test A; NCT-B: Number connection test B; NNT: Number Needed to Treat; OHE: Overt hepatic encephalopathy; PCT: Picture completion test; SDT: Serial dotting test.

by stimulating the growth and activity of the colon bacteria. The addition of insoluble fiber may potentiate the effects of disaccharides through acidification of the colonic lumen by the process of fermentation, which in turn, decreases the production of ammonia[42]. The increase in dietary fiber has been proposed as an alternative for the treatment of patients with MHE (Table 3); reversion of MHE has been reported in 50% of patients treated with symbiotics and fermentable fibers or simply fermentable fibers and in only 13% of patients treated with placebo[29].

Probiotics/symbiotics

The beneficial effects of the administration of probiotics and symbiotics on different variables related to MHE have been confirmed (Table 3). The mechanisms of action include displacement of gas-forming bacteria, inhibition of pathogenic bacteria adhesion, modulation of the immune response, and microbiota modification through the colonic acidification following fiber fermentation[43]. The colonization of the intestine by probiotics that compete against ammonia-producing microorganisms and the concomitant use of probiotics and prebiotics (symbiotics) may cause synergistic effects on the host by decreasing the colonic pH *via* fermentation and less colonization of ammonia-producing bacteria, resulting in decreased ammonemia[29].

Following a 60-d trial of consuming a probiotic yogurt, 70.58% of the patients with MHE reversed this condition, and none did in the control group. Despite having assessed treatment compliance in the probiotic yogurt group, this was not done in the control group nor were other dietary components controlled that could have affected the results[44]. The administration of VSL#3 led to reversion of MHE in 35% of patients and 10% in the placebo group after 3 mo of treatment[40]; after 8 wk of treatment, normalization of the CFF values were achieved in 8.68% of patients in the treatment group *vs* 2.28% in the placebo group[40].

The supplementation of symbiotics (*Pediococcus pentoseceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* subspecies *paracasei* 19, and *Lactobacillus plantarum* 2592, and fermentable fiber; inulin, pectin, beta glucan, and resistant starch) for 1 mo decreased the mean ammonia 36.1% with respect to the mean basal concentrations, while treatment with fermentable fibers decreased this mean 34.7% in the same period; placebos only decreased this mean concentration in 3.14% [29]. Furthermore, when the basal values of endotoxins were considered in these three groups, a mean reduction was achieved in 24.7%, 38.89%, and 4.5%, respectively[29]. Similar results could be observed after 90 d of treatment with *Bifidobacterium longum* and fructooligosaccharides, where the mean decrease in ammonemia was 42.69% with respect to the basal concentration and 10.44% in the placebo group[45].

The importance of treating MHE underscores the possibility of avoiding a future OHE episode. In patients with liver cirrhosis without previous HE episodes and treated prophylactically with VSL#3 for a 3-mo period, the number needed to treat (NNT) for the group of patients with MHE was 5 *vs* 13 in those without MHE to avoid an OHE episode[46].

Non-absorbable disaccharides

In most of the studies on patients with MHE, the effects of lactulose have also been assessed (Table 4). The mechanisms of action of this synthetic disaccharide are mainly related to its cathartic effects, which allow for the reduction of intestinal transit, and therefore, the content of toxic compounds in its lumen and absorption. Along its colonic transit, lactulose is metabolized by bacteria, decreasing the colonic pH. This in turn, renders a hostile environment to urease-producing bacteria together with the increased growth of *Lactobacillae* and *Bifidobacteriae*, which reduce ammonia production in the colonic lumen and interfere with its absorption and that of other nitrogenous compounds produced in the intestine[45,47].

A 4-wk treatment with lactulose enables reversion of MHE in 54.2% of patients compared to 12% in the control group[48]; after 60 d of treatment, the reported reversion increased up to 69.5% in the lactulose group *vs* 21.4% in the placebo group in a per protocol analysis set[49]. Reversion after a 3-mo treatment with lactulose is estimated at 47.5% and 10% in the group receiving the placebo[39].

The treatment of MHE with lactulose also decreases the mean ammonia concentration an approximate 23.03%-32.25% after 1 mo of treatment and 28.66% with the concomitant use of probiotics and lactulose[48,50]. In another study where patients with MHE were followed for 2 mo, the mean decrease of ammonia was 22.1% considering the basal concentrations of the treated group; there was also an increase in 10.46% in the placebo group, $P < 0.001$ [51]. Treatment of lactulose for 3 mo achieved a decrease between 23% and 79% considering the basal ammonia concentrations, rendering an average decrease of 63.16 $\mu\text{mol/L}$ [49,52-54]. When the decrease was analyzed as a categoric variable, the improvement rate in the ammonia concentration in 14 patients was attested to in 6/7 of them (85.7%) when lactulose was administered *vs* 4/7 (57.4%) when patients were treated with lactose[55]. Another change observed after administration of lactulose in patients suffering from MHE has been the decrease in mean basal concentrations of inflammatory factors such as tumor necrosis factor alpha (17.29%), IL-6 (29.54%), IL-18 (32.14%), and endotoxins (36.76%) after a 3-mo treatment[52].

After the use of lactulose for 3 mo, positive changes in some variables related to sleeping such as total sleeping time, sleep efficiency, sleep latency, awake time, and latency rapid eye movement were found[54]. According to some tools that measure QOL such as the sickness impact profile, there is improvement in the overall score and within each of the categories after lactulose administration; however, the study does not describe if any of the patients had alterations in their QOL at the time of being included in the study[49,56].

When endpoints such as the prevention of an OHE episode were considered, patients with liver cirrhosis and no previous HE episode who were treated prophylactically with lactulose for a year showed a decreased incidence; however, the impact of the treatment was greater in those having MHE (NNT in no MHE patients: 50; NNT in MHE patients: 5)[57].

Certain characteristics of patients with MHE lead to lack of response to lactulose treatment. These include hyponatremia, which is prevalent among 50% of the non-responders, and a high basal ammonia concentration[58].

Some alterations that may be detected at the beginning of the treatment with lactulose are diarrhea, flatulence, abdominal bloating, distaste for lactulose, and nausea[11,48,55,59,60]. Diarrhea and flatulence may be reduced after adjusting the lactulose dose[60].

Non-absorbable antibiotics

Rifaximin is a non-absorbable antibiotic that modifies the abundance of bacteria and the intestinal bacterial metabolism. The administration of rifaximin in patients with MHE (Table 5) improves consciousness and decreases the degree of endotoxemia[61]. Rifaximin further reduces ammonemia and improves the psychometric tests more than non-absorbable disaccharides[59].

Use of rifaximin for 2 and 12 wk led to reversion of HE in 52.63% and 73.7%, respectively, while the group treated with lactulose during the same time period reverted it in 40.0% and 69.1% of cases[39]. Similar results were reported with rifaximin as a therapy in a different population of patients with MHE after 2 wk of follow-up. Reversion was reached in 57% of the patients, and when the follow-up was extended to 8 wk, reversion was observed in 75.5%. The group without this treatment reverted HE in 18% and 20% of the patients after 2 and 8 wk, respectively[56]. Response to an 8-wk treatment according to the normalization of the CFF values happened in 6.5% of the patients who underwent treatment *vs* 2.28% in patients included in the placebo group[40].

In a study including subjects with SIBO and MHE, a reversion was found in 42.3% of these patients after a week of rifaximin treatment; however, this result was not contrasted against a control group[27]. A reduction in the mean ammonemia of 24.22% with respect to the basal concentrations was found in a population with similar characteristics, while in patients with MHE and no SIBO there was a reversion in 18.5% after a week of treatment[27]. In yet another study in subjects where the SIBO status was not specified, ammonemia following an 8-wk treatment with rifaximin decreased 7% [61]. A quantitative improvement in terms of scores for QOL were also observed in patients with MHE treated with rifaximin[49,56].

Some studies that evaluated specific endpoints following the suspension of rifaximin and lactulose in patients originally treated for MHE did not find a difference on the rate of OHE development (7.14% *vs* 7.89%)[56,59,62].

Until now, the use of rifaximin has been associated with epigastric discomfort and vomiting in a few patients[56].

DISCUSSION

Prevention and treatment of MHE have been the subjects of many clinical trials. However, the lack of a standard of reference for its diagnosis, the impossibility of observing the impact of a simple maneuver over the reversion of MHE or surrogate variables, and the inclusion of multiple endpoint variables to evaluate the effects of these therapies represent challenges for their overall analysis[63]. Thus, result interpretation of each one of the studies should consider the diagnostic tool that was used, the heterogeneity of the patients regarding their demographic data, the level of schooling, history of previous decompensation, previous episodes of encephalopathy, the hepatic functional reserve, the dietary plan or the indication of concurrent treatments accompanying the experimental treatment, as well as the risk factors that predispose to MHE, such as hyponatremia, sarcopenia, hyperammonemia, the presence of SIBO or dysbiosis, because each one of these factors may potentially modify the novel treatment outcome[7,19,21,23,58].

Regarding the outcome, the assessment of the MHE reversion or the incidence of OHE, when performed through standardized tests, may report clinical utility. However, when results are referred as surrogate variables, such as the improvement in raw values of some psychometric tests, the decrease in blood ammonia concentrations, the changes in the prevalence of SIBO or qualitative data on microbiota in patients with MHE, the real impact on these variables are difficult to interpret. To date, few studies include outcomes related to changes in QOL and mortality.

CONCLUSION

There are currently different alternatives for the treatment of MHE. Prevention should probably be based on diets that provide adequate energy, protein, dietary fiber, and food sources for probiotics to enhance their therapeutic potential without causing the side effects of pharmacological therapies and avoiding the development of sarcopenia. The treatment for the reversion of MHE and its secondary prevention should be tailored for each individual and use pharmacological options of proven efficacy such as lactulose or rifaximin. The implementation of randomized clinical trials that establish the optimal duration of the treatment and its impact on the QOL and job performance as well as the analysis of the cost-benefit of every treatment for MHE are warranted.

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