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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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].

### INTRODUCTION

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].

### ASSESSMENT OF MHE

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 |
|---------------------|-----------------------|
| ISHEN               | Unimpaired            |
|                     | Covert hepatic encephalopathy |
|                     | Overt hepatic encephalopathy |
| WHC                 | No encephalopathy, no history of OHE |
|                     | Imperceptible cognitive alterations during routine clinical examination |
|                     | Trivial lack of awareness; Euphoria or anxiety; 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 |

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[7,21,25]. 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\[41\].
| Ref. | Study type | Follow-up (wk) | MHE diagnosis | Active treatment (s) | Objectives | Patients (n) | Main results/impact measures |
|------|------------|----------------|---------------|----------------------|------------|--------------|-----------------------------|
| Kato et al [37], 2012 | Quasi-experimental | 8 | NCT-A, NCT-B, BDT, DST | 30-35 Kcal + 1.0-1.5 g/kg of protein/d | Reversal of MHE | 19 | 11/19 (57.8%) recovered at 4 wk, and 13/19 (68.4%) at 8 wk |
| Maharshi et al [33], 2016 | Randomized2 | 24 | NCT-A/FCT-A, NCT-B/FCT-B, DST, LTT, SDT | Nutritional education/no nutritional therapy | Reversal of MHE | 60/60 | 27/38 (71.1%) vs 8/35 (22.8%), 27/60 (45%) vs 8/60 (13.3%) when considering PPS and ITT analysis. |
| Malaguarnera et al [64], 2008 | Randomized, double-blind | 13 | NCT-A, NCT-B, BDT, SDT, TMT, AVL, EGG | Acetyl-L-carnitine/placebo | Cognitive scores | 60/55 | Changes of mean values in at least 20.71% to 32.79% respect to basal values |
| Bajaj et al [34], 2014 | Randomized, double-blind | 8 | NCT-A, NCT-B, DST/BDT | LGG/placebo | Psychometric scores | 18/19 | Improvement from 1.02% to 15.89% from baseline values |
| Bajaj et al [44], 2008 | Randomized2 | 8 | NCT-A, BDT, DST | Probiotic yogurt/no treatment | Reversal of MHE | 17/8 | ITT analysis: Reversal in 12/17 (70.58%) vs 0/7 (0%) |
| Mittal et al [39], 2011 | Randomized2 | 12 | NCT-A/FCT-A, NCT-B/FCT-B, BDT, PC | Lactulose/VSL#3, LOLA/no treatment | Reversal of MHE | 40/40/40 | ITT analysis: Reversal of 4 (10%) in no treatment group, 19 (47.5%), 14 (35%) and 14 (35%) |
| Possible history of OHE1 | | | | | | | |
| Egberts et al [36], 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 |
| Ndraha et al [34], 2011 | Double blind, randomized | 2 | CFF | BCAAs + LOLA/BCAAs4 | CFF | 17/17 | Improvement in CFF 7.0% and 1.96% values (Hz), respect to baseline |
| Kircheis et al [41], 1997 | Randomized, double-blind | 1 | NCT-A | LOLA infusion vs placebo | Psychometry | 26/27 | Improvement in mean time to respond NCT-A from baseline (29% vs 9.73%) |
| Liu et al [29], 2004 | Randomized2 | 4 | NCT, BAEP | Symbiotics + fermentable fibers/fermentable fibers/placebo | Reversal of MHE | 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 vs placebo (P = 0.03) |
| Dhiman et al [65], 2014 | Double blind, randomized | 24 | NCT-A/FCT-A, NCT-B, SDT, DST, LTT | VSL#3/placebo | Psychometric scores | 16/13 | Mean psychometric scores before and after probiotics -9.9 (13.3- to 6.5) vs -5.7 (-8.4 to 2.9) P = 0.014. Proportion of patients with scores < -5 did not change in either group |
| Malaguarnera et al [65], 2007 | Randomized, double-blind | 17 | TMT-A, TMT-B, BDT, MMSE | Bifidobacterium longum + FOS/placebo | Psychometry | 30/30 | No statistical or clinical change was found respect to basal values at, 30, 60, 90 and 120 d |
| Ziada et al [48], 2013 | Randomized2 | 4 | NCT-A, DST, SDT | Lactulose/L. acidophilus/control | Psychometry | 24/26/25 | Normalization of test occurred in 13/24 (54.2%), 14/26 (53.8%), and 3/25 (12%) |
Studies in which the clinical history to the OHE events is specified or no is specified within the inclusion criteria.

Unblinded study.

The effect of other treatments for MHE was not studied.

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

Diet was not standardized together with the suggested treatment.

The treatment that the control group received was not specified.

Secondary objectives within the study.

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

Addition of the effect of two maneuvers.

MHE 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 |
|------|------------|----------------|---------------|----------------------|------------|--------------|----------------------------|
| Prasad et al [47], 2007 | Randomized | 12 | NCT-A/FCT-A, NCT-B/FCT-B, P300ERP | Lactulose vs no treatment | Psychometry | 31/30 | ITT analysis: Improvement in 20/31 (64.5%) vs 2/30 (6.7%); NNT:2 |
| Horsmans et al[50], 1997 | Randomized, double-blind | 2 | NCT, RTT. | Lactulose vs lactose as placebo | Psychometry | 7/7 | Improvement in time on Psychometric test on lactulose group respect to basal values. Rate of improvement NCT: 5/7 (71.42%) vs 1/7 (14.28%); NNT:2 |
| Sharma et al [51], 2008 | Randomized | 4 | NCT-A/FCT-A, NCT-B/FCT-B, P300ERP | Lactulose, probiotics, and lactulose + probiotics | Psychometry, P300ERP | 35/35/35 | Normalization in 17/31 (54.8%), 16/31 (51.6%), and 17/30 (56.6%) of MHE patients |
| Morgan et al [60], 1989 | Cross-over, randomized | 8 | EEG, NCT, DST, DCT | Lactulose vs lactitol | Psychometry | 14/14 | No differences between treatments in median change in psychometric time or scores |
| Dhiman et al [51], 2000 | Randomized | 12 | NCT-A/FCT-A, NCT-B/FCT-B, P300ERP | Lactulose vs no lactulose | MHE improvement | 14/12 | Improvement in 8/10 (80.0%) vs 0/8 (0.0%); P < 0.001 |
| Wang et al [49], 2019 | Randomized | 8 | NCT-A, DST | Lactulose vs no lactulose | MHE reversal | 67/31 | ITT analysis: 43/67 (64.2%) vs 7/31 (22.6%); NNT: 3PPS: 41/59 (69.5%) vs 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 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; DST: Digit copying test; DCT: 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; P300ERP: Psychometric time or scores.

**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 |
|------|------------|----------------|---------------|----------------------|------------|--------------|-------------------------------|
| Ahluwalia et al.[66], 2014 | Quasi-experimental | 8 | NCT-A, NCT-B, DST, BDS, LTT, SDT, ICT | Rifaximin⁴ | fMRI, ICT, MRS⁵ | 20 | Changes in ICT, improvement of 12% respect to baseline, indicating a better cognition |
| Bajaj et al.[61], 2013 | Quasi-experimental | 8 | NCT-A, NCT-B, DST, BDT, LTT | Rifaximin⁴ | Psychometry⁵ | 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 et al.[67], 2011 | Randomized, single-blinded | 8 | NCT-A, DST, BDT, ICT | Rifaximin/placebo⁴ | 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% vs 61% (NNT: 4); NCT-B 81% vs 33% (NNT: 2); and ICT lures: 76% vs 43% (NNT: 3)⁷ |
| Sidhu et al.[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% vs 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 et al.[62], 2017 | Prospective cohort | 24 | NCT-A, FCT-A, DST, PCT, BDT | Previous intake of Rifaximin compared to lactulose³ | Maintenance of remission for MHE | 42/38 | Still free of MHE: Rifaximin 42.8% vs lactulose 50.0% (NNT: 14) |
| Possible history of OHE¹ | | | | | | | |
| Agrawal et al.[24], 2011 | Quasi-experimental | 1 | NCT, FTC, LTT. | Clarithromycin, Lansoprazole, tinidazole⁴ | Psychometric scores⁵ | 35 | Improvement in 12.7%, 13.3%, and 18.7% respect to baseline mean time in NCT, FCT and LTT, respectively |
| Zhang et al.[27], 2015 | Quasi-experimental | 5 | NCT-A, NCT-B, DST | Rifaximin 1 wk¹⁴ | Reversal of MHE | 26 | After a week, reversal present in 11/26 (42.3%) |
| Sidhu et al.[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% vs 18% (NNT: 3)At 8 wk: Reversal of 75.5% vs 20% (NNT: 2) |
| Sharma et al.[40], 2014 | Randomized¹ | 8 | NCT-A/FCT-A, DST and/or CFF | LOLA/rifaximin/Probiotics/Placebo⁴ | Reversal of MHE⁵ | 31/31/32/30 | ITT analysis: Improvement in CFF values (Hz) from baseline in 11.42%, 6.5%, 8.68%, and 2.28% |

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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.
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 (Pediacoccus 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 Bifidobacteria, 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].

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7Minimal hepatic encephalopathy reversion not measured. BDT: Block design test; CFF: Critical flicker frequency; DST: Digit symbol test; FCT: Figure completion test; FCT-A: Figure completion 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.
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[31]. 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 μmol/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[39].

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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