Management of Covert Hepatic Encephalopathy

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Hepatic encephalopathy is a reversible progressive neuropsychiatric disorder that encompasses a wide clinical spectrum. Covert hepatic encephalopathy is defined as patients with minimal hepatic encephalopathy and Grade I encephalopathy by West-Haven Criteria. Terminology such as “sub-clinical”, “latent”, and “minimal” appear to trivialize the disease and have been replaced by the term covert. The lack of clinical signs means that covert hepatic encephalopathy is rarely recognized or treated outside of clinical trials with options for therapy based on patients with episodic hepatic encephalopathy. This review discusses the current available options for therapy in covert hepatic encephalopathy and focuses on non-absorbable disaccharides (lactulose or lactitol), antibiotics (rifaximin), probiotics/synbiotics and L-ornithine-L-aspartate. (J CLIN EXP HEPATOL 2015;5:S75–S81)

Hepatic encephalopathy (HE) is a reversible progressive neuropsychiatric disorder occurring in patients with significant liver disease. It encompasses a clinical spectrum of symptoms involving psychomotor, intellectual, cognitive, and motor function.¹ Minimal hepatic encephalopathy (MHE) presents with a normal neurologic examination and no obvious clinical signs, but subtle changes in attention, psychomotor speed, and executive decision making.² Prior terminology included “sub-clinical”, “latent”, and “minimal” appear to trivialize the condition. There is abundant evidence in the literature that MHE has a profound impact on quality of life, daily functioning, driving ability,^{3–10} and nearly half of all patients with MHE may be unfit to maintain employment.⁹ Based on the current ISHEN guidelines,¹¹ patients with MHE and Grade I encephalopathy by West-Haven Criteria were re-classified as having covert hepatic encephalopathy (CHE). Since the prevalence of MHE in patients with cirrhosis varies between 30 and 84%,^{12–15}

therapeutic strategies to prevent overt hepatic encephalopathy (OHE) are of major importance.

Treatment options for CHE are derived from prior experience in patients with episodic HE. Given the lack of clinical signs, CHE is rarely recognized or treated outside of clinical trials. Many therapies have been tested based on theories of the pathogenesis of HE. These include N-methyl-D-aspartate antagonists, N-acetylcysteine, anti-inflammatories (cyclo-oxygenase inhibitors), flumazenil, and bromocriptine. However, all have been abandoned because of evidence of lack of efficacy or adverse safety profile. Circulating levels of ammonia and other gut derived toxins are central to the pathogenesis of HE and remain the target of therapy in CHE. The gut microbiota plays an integral role in the production of ammonia and other toxins resulting in oxidative stress/inflammation.^{16–19} It would only seem natural that treatment modalities in CHE would focus on the modulation of the gut flora. Therapeutic strategies for CHE must be extrapolated from MHE trials as CHE is a relatively recent term and no studies on therapy are available at this time. This review discusses the currently available treatment options for CHE.

NON-ABSORBABLE DISSACHARIDES

Lactulose

Lactulose or lactitol are synthetic non-absorbable disaccharides, that are extensively used in the management of OHE. Lactulose is fermented in the colon into acetic and lactic acid resulting in acidification of intestinal contents and conversion of ammonia (NH₃) to ammonium (NH₄⁺). Unlike ammonia, ammonium is not systemically absorbed and is excreted in stool. Lactulose also has a cathartic effect increasing nitrogen excretion by four

Keywords: hepatic encephalopathy, lactulose, rifaximin, probiotics

Received: 7.1.2014; **Accepted:** 19.2.2014; **Available online:** 1.4.2014

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Abbreviations: HRQoL: health-related quality of life; CFF: critical flicker frequency; NCT-A: number connection tests A; NCT-B: number connection tests B; DST: digit symbol test; OCTT: orocecal transit time; FOS: fructo-oligosaccharides; BAEP: brain auditory evoked potential; BDT: block design test; LCT: line tracing test; RCT: race track test; ICT: inhibitory control test; SDMT: Symbol digit modalities test; TMT: Trail making test; SPT: standard psychometric test; NPE: neuropsychological exam; PCT: Picture completion test; FCT-A: Figure connection test-A; PSE: psychometric testing; SDT: serial-dotting test; APT: abnormal psychometric testing

<http://dx.doi.org/10.1016/j.jceh.2014.02.007>

fold.^{20–22} Recommendations supporting lactulose as the preferred therapeutic option in OHE are based on 2001 guidelines which were developed prior to a number of significant trials in alternative therapies such as rifaximin or probiotics.²⁰ In a recent survey, 78% of gastroenterologists have extended the use of lactulose to first line therapy in the treatment of MHE.²³

In a randomized open label trial, lactulose therapy 30–60 mL/day was compared to no treatment in patients with cirrhosis and MHE.²⁴ Compared to the untreated group, there was a significant decrease in the number of abnormal psychometric tests in the group treated with lactulose ($P < 0.0001$). Treatment also demonstrated a significant improvement in the health-related quality of life (HRQoL) vs. those who did not receive lactulose [6.81 vs 0.17 (95% CI, 5.24–8.37) and (95% CI, –0.29 to 0.63), respectively; $P < 0.001$].²⁴ Sharma et al further reported the benefit of lactulose therapy for the primary prevention of OHE in patients with cirrhosis. A total of 120 cirrhotic patients with no prior episode of OHE were randomized to receive lactulose (55 patients, 32/55 with MHE) or no treatment (50 patients, 36/50 with MHE), with progression to OHE assessed over 12 months. MHE was diagnosed by psychometric and critical flicker frequency testing, while the West-Haven Criteria was used to grade OHE. Lactulose protected against the progression to OHE (11% of patient receiving lactulose and 28% in the control group developed OHE, $P = 0.02$) and 66% of the patients diagnosed with MHE responded to treatment. Therefore, lactulose was deemed to be effective in the primary prevention of overt hepatic encephalopathy.²⁵ Congruent with prior results, several other studies have reported an improvement in neuropsychometric tests with various doses and durations of lactulose and lactitol treatment^{25–30} (Table 1).

In a meta-analysis of five studies (total, $N = 170$ patients), lactulose treatment demonstrated a benefit for MHE (RR 0.34, 95% CI, 0.24–0.47; $P < 0.0001$).³¹ Luo et al further corroborated these findings in a meta-analysis of 9 randomized studies (total, $N = 434$ patients). Analysis revealed a significant reduction in the mean number of abnormal neuropsychological tests, blood ammonia levels, progression to OHE (RR: 0.17, 95% CI, 0.06–0.52, $P = 0.002$), and improved HRQoL.³² The results support the safety and efficacy of lactulose treatment for MHE.

Diarrhea, abdominal pain/cramping, nausea, and flatulence are among the most common dose related adverse effects limiting adherence.^{25,28,33,34} In a trial of 128 cirrhotic patients, Kalaitzakis et al reported that daily lactulose had a negative impact on HRQoL.³⁵ The laxative effect and titration to 2–3 soft bowel movements per day make adherence to lactulose classically low.¹² Paradoxically, overuse of lactulose can result in severe dehydration and hyponatremia leading to worsening of HE. Interestingly, a lower serum sodium (less than 132.5 mmol/L) and a higher ammonia level (greater than 93.5 mmol/L) were two pa-

rameters that correlated with lactulose failure.³⁶ Lastly, as stated earlier, all of the trials presented above were completed in MHE; therefore caution should be used when translating this data to CHE.

Antibiotics

The goal of antibiotic therapy remains the suppression of urease producing intestinal organisms, thereby reducing serum levels of ammonia and other gut derived toxins (eg, mercaptans, phenols, oxindole, and short chain fatty acids).^{22,37,38} Oral antibiotics (eg, neomycin, metronidazole, vancomycin, and paromycin) have demonstrated varying degrees of success in the treatment of OHE. However, systemic adverse events including nephrotoxicity, ototoxicity, peripheral neuropathy, antibiotic resistance, and the risk of *Clostridium difficile* colitis and vancomycin resistant enterocolitis (VRE) has limited their role in the treatment of MHE.

Rifaximin

Rifaximin is an oral non-systemic broad spectrum antibiotic that is structurally similar to Rifampin. By binding to bacterial DNA-dependent RNA polymerase, rifaximin inhibits bacterial RNA/protein synthesis. Structurally, the benzimidazole ring limits systemic absorption to 0.4%,³⁹ with the primary mode of excretion via feces and low levels of drug excreted in urine or bile.^{40,41} Concentrated in the gut, rifaximin is presumed to modulate intestinal bacteria, thereby reducing intestinal ammonia and toxin formation.⁴² In a recent open labeled trial, Bajaj et al performed a systems biologic analysis of the microbiome and evaluated cognitive changes after treatment with rifaximin (550 mg bid) in 20 cirrhotic patients diagnosed with MHE. Therapy was associated with improved cognitive function and reduced endotoxemia. Moreover, treatment with rifaximin resulted in a modest change in stool microbiota characterized by a reduction in *Veillonellaceae* and an increase in *Eubacteriaceae*. *Veillonellaceae* are gram negative cocci that are more abundant in the stool of patients with cirrhosis compared to healthy individuals.¹⁶

The initial studies for rifaximin demonstrated its efficacy in the management of OHE. Compared to lactulose, rifaximin is more effective in the treatment of OHE.⁴³ In a randomized double-blind placebo controlled trial (total, $N = 299$ patients) over a 6-month-period, rifaximin (550 mg twice daily) reduced the risk of an episode of OHE and the time to first hospitalization, with no serious adverse events.⁴⁴ Moreover, Neff et al recently showed that rifaximin use for greater than 6 months proved to be effective in the management of HE, especially in patients with MELD ≤ 20 .⁴⁵

Because of its documented safety and efficacy in patients with OHE, the investigation of rifaximin in the

Table 1 Treatment options in MHE and significant findings.

Treatment groups	Study	Number of patients treated/duration	Psychometric test used	Total daily dosage	Significant findings with treatment
Lactulose	Wantabe <i>et al.</i> , 1997 ^{h,28}	22 ^a , 14 ^g /8 weeks	NCT, DST, BDT	45 mL	↓ APT
Lactulose	Horsmans <i>et al.</i> , 1997 ^{h,27}	7 ^a , 7 ^g /15 days	NCT, RCT	60 g	↓ APT
Lactulose	Dhiman <i>et al.</i> , 2000 ^{h,26}	14 ^a , 12 ^g /3 months	NCT, FCT-A/B	30–60 ml	↓ APT
Lactulose	Prasad <i>et al.</i> , 2007 ²⁴	31 ^a , 30 ^g /3 months	NCT-A/B, FCT-A/B	30–60 ml	↓ APT ↑ HRQoL
Lactulose	Sharma <i>et al.</i> , 2012 ²⁵	60 ^a , 60 ^g /12 months	CFF	30–60 ml	↓ Developed OHE ↓ APT
Lactulose	Sharma <i>et al.</i> , 2012 ³⁴	30 ^a , 30 ^g /3 months	NCT – A/B, DST, LCT, SDT. CFF	30–60 ml	↓ APT, ↓ arterial ammonia
Lactulose	Jain <i>et al.</i> , 2013 ⁷³	30 ^a , 30 ^g /3 months	PHES, NCT-A/B, SDT, LCT	30–60 ml	↓ Serum endotoxins, ↓ APT, ↓ serum ammonia, ↓ IL-6/IL-8/TNF-α, ↓ glutamine, ↑ myoinositol, ↑ choline
Rifaximin	Grande <i>et al.</i> , 2010 ^{i,46}	4 weeks	CFF	1200 mg	↓ APT
Rifaximin	Sidhu <i>et al.</i> , 2011 ⁴⁷	49 ^b , 45 ^g /8 weeks	NCT-A, FCT-A, DST, PCT, BDT	1200 mg	↓ APT, ↑ HRQoL
Rifaximin	Bajaj <i>et al.</i> , 2011 ⁴⁸	21 ^b , 21 ^g /8 weeks	NCT-A/B, DST, BDT, ICT	1100 mg	↑ Driving performance (↓ speeding tickets, driving errors, illegal turns), ↓ APT
Synbiotic ^d , fermentable fiber ^e	Liu <i>et al.</i> , 2004 ⁵¹	20 ^d , 20 ^e , 15 ^g /30 days	NCT, BAEP	1 sachet	Both groups: ↓ fecal pH, ↓ venous ammonia, ↓ serum endotoxin, ↓ APT, ↓ Child-Turcotte Pugh classification
Probiotics	Malaguamera <i>et al.</i> , 2007 ⁵²	30 ^c , 30 ^g /90 days	TMT, BDT, SDMT, MMSE	1 packet	↓ Serum ammonium, ↓ APT
Probiotics	Bajaj <i>et al.</i> , 2008 ⁵⁰	17 ^c , 8 ^g /60 days	NCT-A, DST, BDT	1 yogurt	↓ APT
Probiotics	Lunia <i>et al.</i> , 2013 ^{i,55}	42 ^c , 33 ^g /3 months	CFF	3 units	↓ APT, ↓ SIBO, ↓ OCTT, ↓ arterial ammonia
LOLA	Kircheis <i>et al.</i> , 1997 ^{h,57}	63 ^f , 63 ^g /7 days	NCT-A	20 g	↓ APT, ↓ venous ammonia,
LOLA	Ndhaha <i>et al.</i> , 2011 ⁶⁰	17 ^f , 17 ^g /2 weeks	CFF	18 g	↓ APT, unchanged pre-albumin (nutritional status), unchanged urea–creatinine
LOLA	Silva <i>et al.</i> , 2013 ^{i,62}	6 months	NCT-A/B, DST, CFF, DST	15 g	↓ OHE events
Lactulose ^a , probiotics ^c	Sharma <i>et al.</i> , 2008 ⁵³	35 ^a , 35 ^c , 35 ^{a+c} /1 month	NCT-A/B, FCT-A/B	30–60 mL ^a , 3 capsules ^c	All 3: ↓ APT, ↓ venous ammonia, ↓ Child-Pugh class
LOLA ^f , lactulose ^a , probiotics ^c	Mittal <i>et al.</i> , 2011 ⁶¹	40 ^f , 40 ^a , 40 ^c , 40 ^g /3 months	NCT-A/B, PCT	18 g ^f , 30–60 mL ^a , 220 billion CFU ^c	All 3: ↓ APT, ↓ ammonia, ↑ HRQoL
Probiotics ^c , lactulose ^a	Ziada <i>et al.</i> , 2013 ⁷⁴	26 ^c , 24 ^a , 25 ^g /4 weeks	NCTA, DST, SDT	3 capsule ^c , 30–60 mL ^a	Both: ↓ APT, ↓ venous ammonia

↓: decreased; ↑: increased.

^aLactulose.^bRifaximin.^cProbiotics.^dSynbiotic.^eFermentable fiber.^fLOLA.^gPlacebo/no treatment.^hSub-clinical HE.ⁱAbstract.

management of MHE has been a natural progression. A recent randomized double-blinded crossover study demonstrated that rifaximin significantly improved psychometric tests (PHES) and reduced intestinal ammonia production.⁴⁶ Further, the RIME trial demonstrated the benefit of rifaximin in the management of MHE. Patients were randomized to rifaximin (1200 mg/day, $N = 49$) or placebo for 8 weeks with the primary end points being reversal of MHE symptoms and effect on HRQoL.⁴⁷ Intention to treat analysis revealed that at 2 weeks (57.1% (28/49) vs 17.8% (8/45), $P < 0.0001$) and 8 weeks (75.5% (37/49) vs 20% (9/45), $P < 0.0001$) rifaximin significantly reversed MHE compared to placebo, respectively. Treatment further resulted in a significant improvement in both the semi-quantitative (mean reduction in abnormal neuropsychometric tests) and quantitative cognitive scores (reduction in mean Z-scores). HRQoL was concomitantly improved in the rifaximin group compared to placebo ($P < 0.001$) and strongly correlated with improved neuropsychologic scores ($r = 0.376$, $P < 0.01$). Therefore, improvement in cognitive function was associated with better HRQoL. Interestingly, no significant difference was noted in progression to OHE between the two groups. Overall, rifaximin was well-tolerated with no significant adverse events. The results of the RIME trial showed that the benefits of rifaximin could be extended to patients with MHE.

These findings were furthered by Bajaj et al in a randomized double-blind placebo controlled trial assessing the effect of rifaximin on driving performance. Driving and navigations skills are important because they require attention, working memory, and consolidation of various inputs; the very cognitive domains affected in MHE.⁴⁸ Cirrhotic patients diagnosed with MHE received rifaximin or placebo twice daily for 8 weeks. Treatment significantly reduced total driving related errors, specifically speeding tickets and navigation of illegal turns [(total errors, 76% vs 33%, $P = 0.013$); (speeding tickets, 81% vs 33%; $P = 0.005$); (illegal turns, 62% vs 19%; $P = 0.01$)]. Baseline cognitive function significantly improved in the rifaximin group compared to placebo (Z-scores: 1.13 ± 0.2 vs 0.42 ± 0.2 ; respectively, $P = 0.02$), and there was a negative correlation between improvement in mean cognitive scores, total driving errors ($r = -0.3$, $P = 0.05$), and speeding tickets ($r = -0.4$, $P = 0.01$). This suggests that improved cognitive performance resulted in reduced driving related errors. While overall HRQoL at week 8 was not different, there was significant improvement in the psychosocial dimension of the Sickness Impact Profile compared to placebo ($P = 0.04$).

Rifaximin is considered to be safe and well-tolerated. Adherence to rifaximin during treatment is high (greater than 90%), and demonstrates no difference in the most common adverse events—headache, flatulence, and abdominal pain compared to placebo.⁴⁸ Overall, the efficacy of rifaximin in the management of MHE is well documented,

with its safety/tolerability profile making it an ideal candidate for therapy. While the cost of rifaximin therapy remains a limiting factor, progression to OHE has further significant long-term financial implications. One study showed that OHE patients had a shorter hospital stay and lower per patient hospitalization cost when prescribed rifaximin. Future therapy will depend on the cost effectiveness of maintenance rifaximin therapy⁴⁹; and whether these savings can be expanded to patients with CHE.

Probiotics

Probiotics are live microorganisms that alter the balance of intestinal microflora, and synbiotics are probiotics with the addition of fermentable fiber. While their mechanism of action remains uncertain, it is presumed that reducing intestinal bacterial urease activity decreases absorption of ammonia and other gut derived toxins that result in oxidative stress/inflammation. Probiotics are not only efficacious in the treatment of OHE, but demonstrate benefit for MHE.^{50–53} In a placebo controlled trial, synbiotic treatment for 30 days resulted in a decrease in intestinal pH, blood ammonia levels, and reversal of MHE compared to placebo (50.0% vs 13.3%, respectively; $P < 0.05$). Moreover, none of the patients developed OHE in this study.⁵¹ Bajaj et al further reported that probiotic yogurt treatment lead to a reversal of MHE in 71% of patients with non-alcoholic cirrhosis with no progression to OHE.⁵⁰ Consistent with prior findings, patients with MHE in this study had lower baseline HRQoL as determined by 36 item Short Form Health Survey (SF-36). However, probiotic treatment did not convey a significant difference from baseline HRQoL scores and this was likely related to the lack of sensitivity of the SF-36 in assessing HRQoL in patients with MHE.⁵⁰

In another study, cirrhotic patients with MHE received either probiotic, lactulose, or combination of both agents for a period of one month. There was significant improvement from baseline in all neuropsychometric scores and MHE for all three treatment groups ($P \leq 0.05$).⁵³ In a 2011 Cochrane Review of 7 trials, probiotics were efficacious in the treatment of HE, including quality of life, all cause mortality, and the number of adverse events compared to placebo. Congruent with these findings, a subsequent meta-analysis of 9 studies showed a 50% reduction in the relative risk of no improvement in MHE with probiotic treatment.³¹ Specific limitations with this data include the lack of consensus on the diagnosis of MHE and the small number of patients included in the trials; thereby limiting the strength of analysis.⁵⁴ Recently, in an open labeled randomized controlled trial, a total 42 patients diagnosed with MHE were treated with VSL # 3 (3 capsules daily— 10^8 CFU) with a mean follow-up to treatment of roughly 39 weeks. There was 23% absolute risk reduction and 50% reduction in progression to OHE with probiotic use compared to placebo.⁵⁵

Not all studies have shown a benefit from probiotic treatment. In a randomized double-blind placebo controlled trial involving 4 weeks of probiotic therapy, Saji et al showed no improvement in MHE compared with placebo treatment.⁵⁶ The results of this study must be interpreted with caution as MHE was not defined according to consensus guidelines. Probiotics are widely available, with no reported adverse effects, and may represent a long-term treatment option in the management of MHE. Unfortunately, strain specific evidence is lacking with different probiotics used in each trial, making it difficult to generalize recommendations. Therefore, larger studies with a longer duration of follow-up are required with standardization of probiotic formulations.

LOLA (L-ornithine-L-aspartate)

L-ornithine-L-aspartate has been shown to reduce ammonia levels^{57,58} by upregulating glutamine synthetase and urea cycle activity.⁵⁹ L-ornithine and L-aspartate are separately metabolized to form glutamate, which combined with ammonia, results in the formation of glutamine. Therefore, LOLA lowers plasma ammonia concentrations by enhancing metabolism of ammonia to glutamine.⁵⁹

In a meta-analysis, Bai et al evaluated 8 randomized controlled trials (total, $N = 646$ patients—46% diagnosed with MHE) assessing the efficacy of LOLA compared to placebo in patients with cirrhosis. Treatment with LOLA demonstrated a significant improvement in MHE, diminished serum ammonia levels, and no increase in adverse reactions.⁵⁹ Analysis of individual studies revealed a reduction in abnormal neuropsychological testing and increased HRQoL. Further, Ndihara et al reported the effect of LOLA administration on the nutritional status of patients diagnosed with MHE.⁶⁰ All study subjects were provided information regarding appropriate caloric/protein intake. Those receiving LOLA showed a significant decrease in abnormal psychometric testing, but there was no difference in the improvement of nutritional status (measured by pre-albumin) between the groups. In another randomized trial involving 160 patients diagnosed with MHE, 40 patients were treated with LOLA over a 3-month-period. Treatment revealed a significant improvement in reversal of MHE and HRQoL.⁶¹

Recently, in a randomized trial, cirrhotic patients diagnosed with MHE were treated with LOLA vs. placebo over a 6-month-period. Matched for age, Child's score and MELD, patients receiving LOLA showed an improvement in number connection tests B (NCT-B) (3.4 ± 3.4 vs 1.5 ± 2.3 , $P = 0.01$), critical flicker frequency (CFF) (42.2 ± 5.8 vs 45.2 ± 5.8 , $P = 0.02$), and progression to OHE (5% vs 37.9%, $P = 0.016$).⁶² Of significance, there was no difference in the whole psychometric battery evaluation between patients treated with LOLA and placebo.

Generally, administration of LOLA is safe with the most common side effects being nausea, cough, muscle cramps, and less frequently diarrhea.⁶³ Given the small sample size of studies evaluating LOLA, there is a risk of publication bias; therefore the role of LOLA in the management of CHE should be interpreted with caution.

Management Guidelines for Covert Hepatic Encephalopathy

While significant progress has been made in understanding the importance CHE, to date there is no standardized algorithm for diagnosis and treatment. Once patients with cirrhosis develop MHE, they are at a substantial risk of progression to OHE, resulting in a significant burden to the healthcare system and an increased risk of mortality.^{64,65} Studies have consistently shown that patients with MHE have a diminished quality of life, cognitive function, daily function, and driving impairment.³⁻¹⁰ While it was once thought that cognitive impairment with CHE or OHE was reversible, data from studies evaluating medical treatment or liver transplantation suggest that the associated cognitive changes may not be totally reversible.⁶⁶⁻⁶⁸ Moreover, it has been demonstrated that even after therapy and improvement to normal mental status, a single episode of OHE may continue to have residual negative effects on cognitive function.⁶⁶ Therefore, it would only seem logical to consider prophylactic treatment for HE in patients with cirrhosis. Currently, there are no consensus guidelines regarding screening for CHE and there is debate as to the utility of testing all cirrhotic patients as opposed to a limited testing strategy for those patients with evidence of cognitive impairment.^{12,69} There is also a paucity of data regarding the role of prophylaxis in CHE. A recent analysis using motor vehicle accidents as an end point to compare five treatment strategies for MHE suggested that therapy with lactulose was cost-effective and rifaximin was not.⁷⁰ The study limited cost/benefit analysis to an end point of motor vehicle accidents; therefore further research is required. Guidelines by the Practice Parameters Committee of the American College of Gastroenterology for MHE were last published in 2001. Over the last decade, there is compelling evidence that MHE has a negative impact on quality of life and patient well being.³⁻¹⁰ However, the natural history of CHE and the effect of treatment on the overall prognosis of CHE requires further long-term studies.

Given the side effects of therapies such as lactulose and cost of rifaximin, research into alternative treatment only seems logical. Probiotics and LOLA appear to have benefit in CHE although their role in therapy is not clearly defined. Other treatment options such as branched amino acid (BCAA) or flumazenil have been used to treat HE with

limited success.^{71,72} Overall larger randomized trials are necessary to define the best therapeutic option for CHE treatment.

CONFLICTS OF INTEREST

All authors have none to declare.

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