Efficacy of Probiotic Therapy in Preventing Overt Hepatic Encephalopathy.

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Abstract

Background:

Hepatic encephalopathy (HE) is common and is characterized by several neuropsychiatric symptoms ranging from mild impairments in cognitive function to coma, experienced by cirrhotic patients. Advanced encephalopathy or overt hepatic encephalopathy is associated with poor outcomes including increased mortality, but consequences of reduced physical and mental function as well as reductions in quality of life can be just as devastating. The cost of hepatic encephalopathy for the healthcare system is exorbitant. While therapies exist for severe encephalopathy, increasingly researchers are aiming to prevent clinically overt hepatic encephalopathy. There is growing interest in the use of probiotic products, which have an excellent physiological basis to reduce the absorption of ammonia, a key neurotoxin in precipitating encephalopathy. The present review discusses hepatic encephalopathy, the various classifications, and reviews literature for probiotics studying the effects on preventing severe encephalopathy. We subsequently postulate on the potential studies and strategies for research studies moving forward.

AUTHOR CONFLICT OF INTEREST STATEMENT AND INFORMATION

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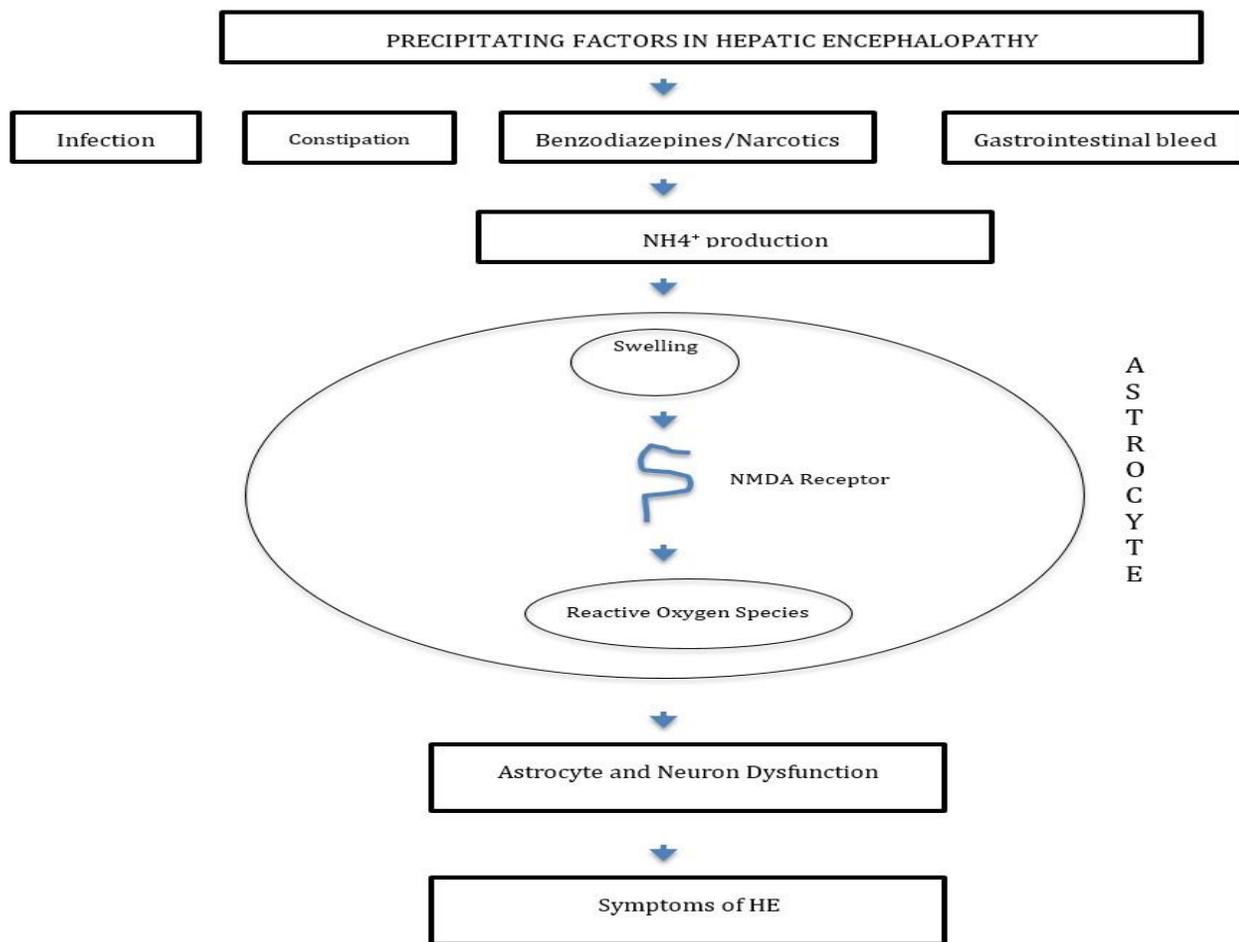
Introduction

Hepatic encephalopathy (HE) is condition of a neuropsychiatric symptoms most commonly associated with liver cirrhosis [1]. Clinically overt hepatic encephalopathy is common and develops in 30-45% of cirrhotic patients [1-3]. This severe and clinically apparent form of this type of encephalopathy is termed overt hepatic encephalopathy (OHE)

and results in marked limitations in functional status, quality of life and increased mortality [1, 4, 5]. While the pathogenesis of HE is complex, ammonia is the most well described neurotoxin in precipitating HE [6]. The gut is the effectively the only source of ammonia, produced by enterocyte metabolism of glutamine [6] and catabolism of protein and urea by colonic bacteria [6]. In cirrhosis, the liver cannot efficiently metabolize ammonia delivered by portal vein into glutamine, which results in entry of ammonia into the systemic circulation [6]. Subsequently, ammonia crosses the blood brain barrier compromising astrocyte function, a critical component in pathogenesis of HE [6-11] (Figure 1).

Standard Therapy for HE

Lactulose is the standard therapy in clinically overt hepatic encephalopathy [12]. It is disaccharide that cannot be catabolized into individual monosaccharides by the small bowel enterocytes, due to lack of specific disaccharidase activity [13]. Lactulose enters the colon unaltered where colonic bacteria then metabolize it into short chain fatty acids lowering the pH. The lower pH favors the formation of the ammonium ion NH_4^+ rather than the absorbable ammonia NH_3, consequently reducing plasma ammonia concentrations [12,13]. However, lactulose is not well tolerated [9]. Moreover, a recent systematic review found that the use of lactulose or was ineffective compared to placebo when considering studies of high methodological quality [13,14]. While other therapies including antibiotic therapy exist, many are not available in Canada, such as rifaximin, and are limited by cost [11] and others limited by efficacy [13] (See Table 1). **Please note that all tables are shown in the appendix after the reference section.**

Potential Role for Probiotics in HE

The need for better, well-tolerated and cost effective therapies have turned the attention of researchers to probiotics. In the most basic definition, are live microorganisms that when given in adequate amounts provide benefit to the host (WHO) these are usually laboratory designed and clinically tested formulations of non pathogenic commensal or food related microorganisms that have beneficial properties for the host [13]. Probiotics offer a powerful pathophysiologic mechanism of meaningful alterations gut flora that may reduce portal vein ammonia absorption by favoring colonization of acid-resistant, non-urease producing bacteria [15].

CLINICAL RELEVANCY STATEMENT

- ➢ *We review hepatic encephalopathy (HE) and the evidence of probiotics in modulating HE.*
- ➢ *We postulate on are areas of focus for studies of probiotic therapy on HE.*

Figure 1. Pathogenesis of Hepatic Encephalopathy [50]

Pathogenesis of Hepatic Encephalopathy: Ammonia, among other entities, induces astrocyte swelling, contributes to N-methyl-D-aspartate (NMDA) receptor activation and subsequent formation of reactive oxygen species ultimately resulting in altered astrocyte dysfunction, and clinical symptoms of hepatic encephalopathy [50].

Last year, researchers from India have completed an open label randomized control trial where they enrolled cirrhotic patients with subtle findings of encephalopathy, appropriately termed minimal hepatic encephalopathy, or MHE. The patients who received commercially available probiotics experienced substantively lower rates of overt hepatic encephalopathy [16].

Buoyed by this recent study we set to review hepatic encephalopathy, the differences and relationship between minimal hepatic encephalopathy and overt hepatic encephalopathy, and to make recommendations about further research in this important field.

Minimal Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric complication occurring in the context of acute or chronic liver dysfunction, portosystemic shunting or any combination of those entities [17]. HE is subcategorized into two separate primary components: overt HE (OHE) and minimal HE (MHE). OHE manifests through a constellation of commonly recognized symptoms, ranging from lack of awareness, shortened attention span and euphoria (grade I) to a coma (grade IV) [17] (Table 2).

More difficult to diagnose is MHE, often termed "subclinical encephalopathy". It is characterized by distinct abnormalities on psychometric examination with a normal neuropsychiatric examination [17]. The prevalence of MHE is approximated at 55% in the setting of cirrhosis [18]. MHE increases the risk of the development of OHE and may have negative consequences on survival [3]. Diminished psychometric performance, evidence of subtle cognitive decline and correlations with driving impairment and increased motor vehicle collisions have been documented with MHE [19-21]. In addition, negative effects on quality of life, decreased executive functioning, impaired memory and sleep disturbances have also been demonstrated with MHE [22-24]. The annual rate of progression from no MHE to MHE in cirrhotic patients is 19% [25].

The diagnosis of MHE can be difficult, and several diagnostic methods have been described, including that of neuropsychological tests, computerized tests and other experimental methods but no ideal test for MHE currently exists. Given this heterogeneity in diagnosis, a Working Party at the 11th World Congress of Gastroenterology recommended that the diagnosis require a normal mental status and impairment in performance in at least two psychometric tests,

including Number Connection Test A and B (NCT-A, NCT-B), Block Design Test (BST) and Digit Symbol Test (DST) [17]. Recommendations were also made to include additional psychometric testing and electroencephalography testing when possible [26]. Given the increasing body of literature demonstrating the negative outcomes in MHE and the potential of conversion to OHE (estimated up to 23% over a one year period [27]), various treatment modalities have been suggested, most of which are aimed at reducing blood ammonia levels. However, MHE is often not treated outside of clinical trials given the difficulty of diagnosis and lack of overt symptomatology. Non-absorbable disaccharides, such as lactulose, have some empiric evidence in improving psychometric tests and possible health-related quality of life (HRQOL) in MHE [28]. Compliance-related side effects often limit the effectiveness of such interventions, due to gastrointestinal complaints and self-titration of therapy to achieve the 2 to 3 bowel movements per day. There is limited randomized data exists documenting the efficacy and cost effectiveness of antibiotics, including rifampin, in MHE.

Impact of Encephalopathy

The burden of hepatic encephalopathy is substantial to both the patient and the healthcare system [29]. Overt hepatic encephalopathy is the second most common reason for hospitalization of cirrhotic patients, and is the most cause for readmission to hospital [30]. Estimates of cost to the healthcare system in Canada are not available but estimates in the United States of America range up to $7 billion per year [31-33]. Moreover, hospital stays are longer (8 days vs. 6.8 days). Even on dischagre, cirrhotics with OHE require more primary care visits (18.2 vs. 8.7 contacts per patient year) when compared to cirrhotic patients without HE [32]. This is particularly relevant as encephalopathy is potentially preventable. The true economic costs may be considerable greater when one considers the effect on employment, managing finances, and resultant burden, both financial and otherwise, on family members and caregivers [33]. Overall, overt hepatic encephalopathy (OHE) is associated with a significant increase in mortality (58.1% vs. 32.4%), when compared to cirrhotics with a similar degree of liver dysfunction [33]. This is reflected in the ChildPugh-Turcotte score which incorporates OHE as a predictor of poor outcomes, and was previously the dominant scoring system utilized in stratifying need for liver transplant [34] (Table 3). The effects of MHE are more subtle. There is a growing body of literature suggesting that MHE has a substantial effect on quality of life, particularly in activities of daily living requiring motor skills, detailed attention and three dimensional visual-spatial ability [35]. MHE can affect driving ability and several experts recommend assessment of driving history in patients with MHE [20].

Review of Literature

The focus of this article is reviewing the literature regarding the use of probiotics both as a treatment of MHE but more importantly, as a prophylactic measure in preventing OHE. We chose to study the effects of probiotics on MHE rather than all cirrhotic patients given the high rates of progression of MHE to OHE. Probiotics may be efficacious in HE by altering intrinsic gut flora via the colonization of non-ureaseproducing organisms, which could subsequently alter levels of gutderived toxins in the blood. This may include decreasing ammonia levels in portal circulation [25]. With that said, measuring MHE reliably and being able to demonstrate improvement in MHE status is difficult, as discussed above. Hence, the potential role of probiotics in study is whether or nor probiotics can decrease the rate of progression of MHE to OHE.

We performed an electronic literature search regardless of language was conducted on electronic databases including The Cochrane CENTRAL Register for Controlled Trials (2014), EMBASE (1980+), Scopus (1990 present), EBSCO host (1960 to 2014), PUBMED / MEDLINE (1966 to 2014), OVID (1950 to 2014). The search strategy used to search was for PUBMED search was modified to search other electronic databases. We only studied randomized control trials, metaanalyses and COCHRANE reviews that evaluated the use of probiotics in MHE [36-44]. The results of this literature are summarized in Table 4. Although probiotics were the predominant form of intervention evaluated in MHE, these should be differentiated from prebiotics and synbiotics, which have also been used in various trials [45]. Prebiotics refers to non-digestible ingredients that stimulate the growth and activity of select bacteria in the gut to improve host health, such as fermentable fiber [45]. Probiotics are a live microbial supplement that selectively improves intestinal microbial balance. Synbiotics are a combination of probiotics and prebiotics [45].

In the past decade, numerous randomized trials have documented the efficacy of probiotics in MHE [36-41] and OHE [44,46-48]. Bajaj *et al.* [37] studied non-alcoholic cirrhotic patients in 25 patients and demonstrated a 71% reversal Of MHE with probiotics vs. 0% in the control group. No patient in the interventional arm developed OHE, as opposed to 25% in the untreated group. They observed excellent adherence to the probiotic regimen. Mittal *et al.* [38] compared probiotics, lactulose and L-ornithine L-aspartate (LOLA), a stable salt derivative that may benefit both OHE and MHE [49], to placebo. Their robust trial with 160 patients demonstrated all three treatment arms were similarly efficacious at significantly improving MHE and HRQOL versus placebo. In 2014, Sharma *et al.* [43] examined 124 cirrhotic patients with MHE and the probiotic arm of the study demonstrated 50% improvement of MHE via improved psychometric scoring, significantly higher that of placebo, but comparable to LOLA and rifaximin. Based on these and other randomized trials listed in Table 4, certainly there is a significant amount of data to suggest that there is a role of probiotics in the treatment of MHE. No significant adverse events were reported with such therapy and compliance was often excellent, which is often in stark contrast to other therapies like lactulose.

McGee *et al.* [42] in 2011 completed a COCHRANE review amassing randomized trials comparing probiotics to placebo or no treatment. They included both OHE and MHE and analyzed a vast array of outcomes. Of the seven trials meeting the inclusion criteria, five assessed MHE. There were no significant differences in all-cause mortality, adverse events, symptom resolution or quality of life when probiotics were compared with both placebo (or no intervention) and lactulose. The authors did not mention specifically how those with MHE improved on probiotics, with respect to psychometric scores. Overall, the quality of evidence was poor with respect to sample size, consistency of reported outcomes, trial populations, and variations in duration of therapy. Thus, meaningful conclusions regarding the benefits and risks of probiotic therapy, specifically in MHE, could not be drawn from this review. Most of the probiotics studied were products from cultured milk products [13]. The list of microorganisms is extensive and includes species and strains of lactic acid bacilli including *Lactobacillus* and *Bifidobacterium*, as well as those strains with a shorter history of therapeutic use in humans, such as *Escherichia coli*, *Clostridium butyricum*, *Streptococcus salivarius*, and *Saccharomyces boulardii*. The most tested species for hepatic encephalopathy appear to be from the *Lactobacillus* and *Bifidobacterium* genera [13]. There is even less literature focusing on the prevention of OHE in the setting of MHE. Of the more robust and recent trials, Lunia et al. in 2014 [44] published an open-labeled, non-blinded, randomized controlled trial with adult cirrhotic patients with MHE and no previous history of OHE,

who were assigned to probiotics (N = 86) versus their control (N = 74). The psychometric hepatic encephalopathy score (PHES) was used to diagnose MHE, which utilizes a variety of psychometric testing to come to the diagnosis. Their study demonstrated a significant decrease in the number of patients with MHE following 3 months of therapy in the probiotic group as documented by improved psychometry, in addition to a reduction in the incidence of small intestinal bacterial overgrowth (SIBO) and reduction of arterial ammonia in the treatment arm. They used commercially available VSL#3 (mixture of non urease-producing organisms including *Streptococcus thermophilus*, and species of *Bifidobacterium* and *Lactobacillus*). The probiotic group also demonstrated a significant reduction in the development of OHE at 8.8% in the probiotic group vs. 20.3% in the control, with a number needed to treat (NNT) of 4.2 (i.e. roughly four patients with cirrhosis and MHE need to be treated with probiotics to prevent one episode of OHE). On multivariate analysis, MHE, the Child-Turcotte-Pugh score correlated significantly with the development of OHE [44].

Discussion

We cannot conclude probiotics would be effective in altering progression of MHE to OHE, based on the absence of quality randomized control data to date. However, there are strong literature pointing to positive signals in improvement of outcomes in reducing progression of MHE to OHE and improvement in MHE with probiotic therapy [44].

We argue that the target population for further studies in probiotics should target patients with MHE. This is because of the high rates of progression of MHE to OHE, which is reported as high as 23% per year [28]. In the most recent trial by Lunia *et al.*, there was a similar progression rate was reported at 20.3% at 40 weeks [44]. While one could argue to target all cirrhotic patients, the need for feasible sample sizes mandate further study in MHE patients only. We would also contend that future studies must target patients with higher Child Pugh scores. The Child Pugh classification includes overt hepatic encephalopathy as a defining of the most severe classification, Child Pugh class C. Several studies have demonstrated that advanced Child Pugh score (i.e. class B versus class A) is an independent predictor of progression to overt hepatic encephalopathy [3].

We would also defend our assertion that future studies be powered to primarily determine if OHE can be prevented rather than to determine if improvements in MHE can be achieved with probiotic therapy. While the burden of MHE cannot be ignored, the modalities utilized to diagnose and monitor MHE are difficult to perform, time consuming and subject to considerable inter-observer variability [14]. Changes in on neuro-psychometric testing do not necessary correlate to improved quality of life or other functional measures in terms of activities of daily living. Moreover, well-formed treatment algorithms do not exist currently. Thus, studies only directed at reducing MHE, will be difficult to design and perform, and interpret. However, what is not in question in that OHE which is clearly defined, easily recognizable with clearly profound consequences for patients, caregivers, and the healthcare system [29,30].

Further study of probiotics is particularly important given the absence of any documented evidence pointing to adverse effects [9] and the devastating short-term and long-term consequences of OHE, as discussed above.

The choice of probiotic to use in a study may be controversial given the heterogeneity of probiotics used, and their may a class effect. However, based on the Lunia study and the results of previous reviews we would recommend probiotic products that contain *Lactobacilli* and Bifidobacteria [13].

Conclusion

Minimal hepatic encephalopathy poses numerous hazards to the cirrhotic patient, namely that of conversion to OHE and other risks, including that of driving impairment and cognitive decline. Based on the aforementioned literature, there is a growing body of literature supporting the use of probiotics in MHE. Multiple randomized studies have demonstrated improved psychometric scoring and resolution of MHE with such therapy. There is less, but very promising, literature documenting the use of probiotics as prophylaxis against conversion of MHE to OHE. Probiotics have had no significant documented adverse effects and compliance appears to be excellent, which is often not the case with alternative therapies such as lactulose. Ultimately, further randomized and blinded studies with larger sample sizes would help to reinforce the practical use of probiotics in the prophylaxis of progression of MHE to OHE.

References

1. Ferenci, P. Hepatic encephalopathy in adults: Clinical manifestations and diagnosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed July 27, 2014.
2. Boyer T, Haskal Z. The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. Hepatology, 2005. 41:386.
3. Romero-Gómez M, Boza F, García-Valdecasas M, et al, Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol, 2001. 96:2718.
4. Bustamante J., Rimola A, Ventura P, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol, 1999. May 1999;30(5):890-5.
5. Ferenci P. Hepatic encephalopathy. In: Haubrich WS, Schaffner F, Berk JE, eds. Bockus Gastroenterology. 5th ed. Philadelphia, Pa: WB Saunders, 1995. 1998-2003.
6. Ferenci, P. Hepatic encephalopathy: Pathogenesis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed July 27, 2014.
7. Grippon P, Lafitte MLP, Boschat M, et al. Evidence for the role of ammonia in the intracerebral transfer and metabolism of tryptophan. Hepatology, 1986. 6:682.
8. Balata S, Damink SW, Ferguson K, et al. Induced hyperammonemia alters neuropsychology, brain MR spectroscopy and magnetization transfer in cirrhosis. Hepatology 2003;37:931–9.
9. Cordoba J, Alonso J, Rovira A, et al. The development of lowgrade cerebral edema in cirrhosis is supported by the evolution of (1)H-magnetic resonance abnormalities after liver transplantation. J Hepatol 2001;35:598–604.
10. Lockwood AH, Yap EW, Wong WH. Cerebral ammonia metabolism in patients with severe liver disease and minimal HE. J Cereb Blood Flow Metab 1991;11:337–41.
11. Shawcross DL, Davies NA, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. J Hepatol. 2004;40:247–54.
12. Sharma P, Sharma B. Disaccharides in the treatment of hepatic encephalopathy. Metab Brain Dis, 2013. 28:313.
13. Ferenci P. Hepatic encephalopathy in adults: Treatment. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed July 27, 2014.
14. Als-Nielsen B, Gluud L, and Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. Cochrane Database Syst Rev, 2004. CD003044.
15. Liu Q, Duan Z, Ha D, et al. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology 2004. 39:1441.
16. Lunia, M, Sharma B, Sharma P, et al. Clin Gastroenterol Hepatol. Jun;12(6):1003-8, 2014.

17. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy — Definition, nomenclature, diagnosis, and quantification: Final report of the Working Party at the 11 th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002;35:716-21.

18. Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy, ambulant, nonshunted patients with cirrhosis. J Hepatol 1986;3:75-82.

19. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol 2001;96:2718-2723.

20. Bajaj JS, Hafeezullah M, Hoffmann RG, Saeian K. Minimal hepatic encephalopathy: a vehicle for accidents and traffic violations. Am J Gastroenterol 2007;102:1903-1909.

21. Wein C, Koch H, Popp B, Oehler G, Schauder P. Minimal hepatic encephalopathy impairs fitness to drive. Hepatology. 2004;39:739-745.

22. Arguedas MR, DeLawrence TG, McGuire BM. Infl uence of hepatic encephalopathy on health-related quality of life in patients with cirrhosis. Dig Dis Sci 2003;48:1622–6.

23. Cordoba J, Cabrera J, Lataif L, Pener P, Zee P, Blei AT. High prevalence of sleep disturbances in cirrhosis. Hepatology1998;27:339–45.

24. Weissenborn K, Heidenreich S, Giewekemeyer K, Ruckert N, Hecker H. Memory function in early hepatic encephalopathy. J Hepatol 2003;39:320–5.

25. Bajaj, J., S. Pinkerton, A. Sanyal, et al. Diagnosis and treatment of minimal hepatic encephalopathy to prevent motor vehicle accidents: a cost-effectiveness analysis. Hepatology, 2012. Apr;55(4):1164-71.

26. Weissenborn K, Ennen JC, Schomerus H, Rückert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. J Hepatol 2001;34:768–73.

27. Bajaj J. Management Options for Minimal Hepatic Encephalopathy. Expert Rev Gastroenterol Hepatol, 2008. 2(6):785-790.

28. Poordad F. Review article: the burden of hepatic encephalopathy. Aliment Pharmacol Ther, 2007. Feb 2007;25 Suppl 1:3-9.

29. Volk, M., R. Tocco, J. Bazick, et al. Hospital readmissions among patients with decompensated cirrhosis. Am J Gastroenterol, 2012. Feb 2012;107(2):247-52.

30. Stepanova M, Mishra A, Venkatesan C, et al. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. Clin Gastroenterol Hepatol, 2012. Sep 2012;10(9):1034-41.

31. Orr J, Morgan C, Jenkins-Jones S, et al. Resource use associated with hepatic encephalopathy in patients with liver disease. Journal of Hepatology, 2014. 60(1): S228– S229.

32. Bajaj J, Wade J, Gibson D, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. Am J Gastroenterol, 2011. Sep 2011;106(9):1646-53.

33. Morgan C, Jenkins-Jones S, Radwan A, et al. Mortality associated with hepatic encephalopathy in patients with severe liver disease. International Liver Congress 2014. Abstract P452.

34. Child CG, Turcotte JG. The Liver and Portal Hypertension. Philadelphia, WB Saunders Co. 1964.

35. S. Prasad, Dhiman RK, Duseja A, et al. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. Hepatology, 45 (2007), pp. 549–559.

36. Saji S, Kumar S, Thomas V. A randomized double blind placebo controlled trial of probiotics in minimal hepatic encephalopathy. Trop Gastroenterol, 32 (2011), pp. 128–132.

37. Bajaj JS, Saeian K, Christensen KM, et al. Probiotic yogurt for the treatment of minimal hepatic encephalopathy. Am J Gastroenterol, 103 (2008), pp. 1707–1715.

38. Mittal VV, Sharma BC, Sharma P, et al. A randomized controlled trial comparing lactulose, probiotics, and Lornithine L-aspartate in treatment of minimal hepatic encephalopathy. Eur J Gastroenterol Hepatol, 23 (2011), pp. 725–732.

39. Sharma P, Sharma BC, Puri V, et al. An open label randomised controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. Eur J Gastroenterol Hepatol, 20 (2008), pp. 506–511.

40. Malaguarnera M, Greco F, Barone G, et al. Bifidobacterium longum with fructo-oligosaccharide (FOS) treatment in minimal hepatic encephalopathy: a randomized, doubleblind, placebo-controlled study. Dig Dis Sci, 52 (2007), pp. 3259–3265.

41. Shukla S, Shukla A, Mehboob S, et al. Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy. Aliment Pharmacol Ther, 33 (2011), pp. 662–671.

42. McGee RG, Bakens A, Wiley K. Probiotics for patients with hepatic encephalopathy. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD008716.

43. Sharma K, Pant S, Mirsa S, et al. Effect of rifaximin, probiotics, and l-ornithine l-aspartate on minimal hepatic encephalopathy: A randomized controlled trial. Saudi J Gastroenterol. 2014 July-August;20(4):225-232.

44. Lunia MK, Sharma BC, Sharma P, et al. Probiotics prevent hepatic encephalopathy in patients with cirrhosis: a randomized controlled trial. Clin Gastroenterol Hepatol. 2014 Jun;12(6):1003-8

45. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr. 1995; 125: 1401–12.

46. Malaguarnera M, Gargante MP, Malaguarnera G, et al. Bifidobacterium combined with fructo-oligosaccharide versus lactulose in the treatment of patients with hepatic encephalopathy. Eur J Gastroenterol Hepatol, 22 (2010), pp. 199–206.

47. HolteK, Krag A, Gluud LL. Systematic review and metaanalysis of randomized trials on probiotics for hepatic encephalopathy. Hepatol Res, 42 (2012), pp. 1008–1015.

48. Agrawal A, Sharma BC, Sharma P, et al. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open label, randomized controlled trial of lactulose, probiotics, and no therapy. Am J Gastroenterol, 107 (2012), pp. 1043–1050.

49. Bai M, Yang Z, Qi X, et al. L-ornithine-l-aspartate for hepatic encephalopathy in patients with cirrhosis: a meta-analysis of randomized controlled trials. J Gastroenterol Hepatol. 2013 May;28(5):783-92.

50. Perazzo JC, Tallis S, Delfante A, et al. Hepatic encephalopathy: An approach to its multiple pathophysiological features. World J Hepatol. 2012 March 27; 4(3): 50-65.

Appendix

Table 1: Standard and Newer Medical Treatments of Hepatic Encephalopathy

Therapy	Mechanism of Action	Evidence	Limitations and Side Effects
Lactulose	Disaccharide laxative metabolized by colonic flora, lowering pH, favoring the formation of ionized ammonium ion, $NH4^+$, decreasing ammonia absorption	-Limited evidence pointing to lactulose being more effective than placebo in treatment of HE and prevention of recurrent of HE. -No effect on survival. -Limited evidence for improvement in HR-QOL and cognition in MHE.	-Gas bloat symptoms, cramping and diarrhea result in compliance issues. - Difficult to self-titrate bowel movements
Rifaximin	Antibiotic resulting in altered gut flora, affecting ammonia production	-Some efficacy in HE and prevention of recurrent HE; similar to lactulose -No survival benefit. Improved HR-QOL and simulated driving tests in MHE.	- Cost over $1000 per month. - Bacterial resistance.
Neomycin	Antibiotic resulting in altered gut flora, affecting ammonia production	- Very limited data suggesting efficacy	-Ototoxicity -Nephrotoxicity - Bacterial resistance
Metronidazole	Antibiotic resulting in altered gut flora, affecting ammonia production	- Very limited data suggesting efficacy	Neurotoxicity/peripheral neuropathy
LOLA (Oral L-ornithine-L-aspartate)	Promotes conversion of ammonia to glutamine, thereby lowering plasma ammonia concentration	- Very limited data suggesting efficacy	- Not widely available

HR-QOL = Health-related Quality of Life. MHE = Minimal Hepatic Encephalopathy.

Table 2: Grades of Hepatic Encephalopathy [1,6,17]

Points:	Encephalopathy	Ascites	Bilirubin	Albumin	Prothrombin Time Prolongation
1	None	Absent	<2 md/dL	>3.5 g/dL	<4 seconds above control (INR <1.7)
2	Grade 1 or 2	Slight	2-3 mg/dL	2.8-3.5 d/dL	4-6 seconds above control (INR 1.7-2.3)
3	Grade 3 or 4	Moderate	>3 mg/dL	<2.8 g/dL	>6 seconds above control (INR >2.3)
Child-Pugh Class → A: 5-6 points, B: 7-9 points, C: 10-15 points					

Table 3: Grades of Hepatic Encephalopathy [1,6,17]

Points:	Encephalopathy	Ascites	Bilirubin	Albumin	Prothrombin Time Prolongation
1	None	Absent	<2 md/dL	>3.5 g/dL	<4 seconds above control (INR <1.7)
2	Grade 1 or 2	Slight	2-3 mg/dL	2.8-3.5 d/dL	4-6 seconds above control (INR 1.7-2.3)
3	Grade 3 or 4	Moderate	>3 mg/dL	<2.8 g/dL	>6 seconds above control (INR >2.3)
Child-Pugh Class → A: 5-6 points, B: 7-9 points, C: 10-15 points					

Table 4: Summary of Control Trial Evidence of Probiotics in MHE

Study	Year	Trial Design	Findings
Liu *et al.* [15]	2004	Cirrhotics with MHE, randomized to synbiotics, fermentable fiber alone or no therapy for one month, N = 55.	Significant reversal of MHE and improvement of Child-Turcotte-Pugh score in 50% in synbiotic group.
Malaguarrera *et al.* [40]	2007	Cirrhotics with MHE, randomized to probiotics or placebo for 90 days, N = 60	Probiotic group had significantly decreased fasting ammonia levels, significantly improved Trail Making Test A and B, DST and MMSE.
Bajaj *et al.* [37]	2008	Non-alcoholic MHE cirrhotics, non-blinded, randomized, to probiotic yogurt vs. no treatment for 60 days, 2:1 ratio, N = 25.	Probiotic arm had significant improvement in NCT-A, BDT, DST. Excellent adherence.
Sharma *et al* [39]	2008	Cirrhotics with MHE, randomized to lactulose 30-60mL/day, probiotics or combined therapy for 1 month, N = 105.	Normalization of psychometry and resolution of MHE in 51.6% of probiotic group, 56.6% of combined group and 54.8% in lactulose group; all equally effective.
Mittal VV *et al.* [38]	2011	Cirrhotics with MHE, randomized to no treatment, lactulose 30-60mL twice per day, LOLA or probiotics for 3 months, N =160	Probiotic arm had significantly improved MHE with improved SIP scores and improved HRQOL; similar results seen in LOLA and lactulose arms.
Shukla *et al.* [41]	2011	Meta-Analysis: 9 RCT's of cirrhotics with MHE, randomized to any of prebiotics, probiotics and synbiotics and lactulose	Prebiotics, probiotics and synbiotics showed significant improvement of MHE, as did lactulose. The best efficacy was that of lactulose and probiotics.
McGee *et al.* [42]	2011	Cochrane Review: 7 RCT's, 5 of which included MHE, comparing probiotics to placebo, no intervention or lactulose. N = 500. Primary outcomes included: mortality, recovery of encephalopathy, adverse events and QOL.	No convincing evidence of clinically efficacious or harmful effect of probiotics in any arm. Trials had high risk of bias and random errors. Specific evaluation of psychometric outcomes was not compared.
Sharma *et al.* [43]	2014	Cirrhotics with MHE, randomized to rifaximin, probiotics, LOLA or placebo for 2 months, N = 124.	Probiotics improved MHE in 50% vs. 67.7% with LOLA, 70.9% for rifaximin and 30% for placebo. All were significantly better than placebo.
Lunia *et al.* [44]	2014	Cirrhotics with MHE, randomized to probiotics or placebo for 3 months, N = 160	Probiotic group: significantly reduced ammonia levels and improved MHE. Also significant reduction in patients developing OHE.