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MINIREVIEWS

Role of gut microbiota in the pathogenesis and therapeutics of minimal hepatic encephalopathy *via* the gut-liver-brain axis

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Abstract

Minimal hepatic encephalopathy (MHE) is a frequent neurological and psychiatric complication of liver cirrhosis. The precise pathogenesis of MHE is complicated and has yet to be fully elucidated. Studies in cirrhotic patients and experimental animals with MHE have indicated that gut microbiota dysbiosis induces systemic inflammation, hyperammonemia, and endotoxemia, subsequently leading to neuroinflammation in the brain *via* the gut-liver-brain axis. Related mechanisms initiated by gut microbiota dysbiosis have significant roles in MHE pathogenesis. The currently available therapeutic strategies for MHE in clinical practice, including lactulose, rifaximin, probiotics, synbiotics, and fecal microbiota transplantation, exert their effects mainly by modulating gut microbiota dysbiosis. Microbiome therapies for MHE have shown promised efficacy and safety; however, several controversies and challenges regarding their clinical use deserve to be intensively discussed. We have summarized the latest research findings concerning the roles of gut microbiota dysbiosis in the pathogenesis of MHE *via* the gut-liver-brain axis as well as the potential mechanisms by which microbiome therapies regulate gut microbiota dysbiosis in MHE patients.

Key Words: Gut microbiota; Minimal hepatic encephalopathy; Gut-liver-brain axis; Pathogenesis; Therapeutics

Core Tip: Minimal hepatic encephalopathy (MHE) is a common neuropsychiatric complication of liver cirrhosis. Gut microbiota dysbiosis has an essential role in the pathogenesis of MHE *via* the gut-liver-brain axis. Current therapeutic strategies for MHE are based on the modulation of gut microbiota dysbiosis. This review presents the recent evidence on the roles of gut microbiota dysbiosis in the pathogenesis and treatment of MHE *via* the gut-liver-brain axis.

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INTRODUCTION

Hepatic encephalopathy (HE) is a central nervous system complication of chronic liver disease or portal systemic shunting that is characterized by a broad range of neuropsychiatric symptoms[1]. Depending on the severity of clinical manifestations, HE can be classified as overt or covert, such as minimal HE (MHE) and West Haven grade I HE[1]. Overt HE (OHE) exhibits obvious neurological and psychiatric manifestations, such as flapping tremors, drowsiness, and sometimes coma[2]. In contrast, MHE presents with slight cognitive deficits in the executive function, including psychomotor speed, response inhibition, and working memory, with no clinical evidence of OHE[3]. MHE is diagnosed using neurophysiological and psychometric tests, and its prevalence range from approximately 30% to 70% in different populations with liver cirrhosis[1,3,4]. MHE compromises daily functions, affects the health-related quality of life, and increases the risk of progression to OHE[5,6].

The exact pathogenesis of MHE is complex and not completely understood. Furthermore, the pathophysiological basis of MHE is multifactorial, with ammonia, inflammation, and endotoxins considered causative factors[7]. Recently, gut microbiota dysbiosis has been demonstrated to be associated with hyperammonemia, systemic inflammation, neuroinflammation, and endotoxemia in cirrhotic patients and experimental animals with MHE[8-11]. With decompensated liver cirrhosis and hepatic dysfunction, dysbiotic gut microbiota and its metabolites cross the impaired intestinal barrier and induce hyperammonemia, systemic inflammation, and endotoxemia, which influence the permeability of the blood-brain barrier (BBB), resulting in neuroinflammation and low-grade edema in the cerebrum and contributing to central nervous system dysfunction[7]. It has been increasingly recognized that gut microbiota dysbiosis is the predominant factor accounting for MHE pathogenesis *via* the gut-liver-brain axis[12,13]. Furthermore, an increasing number of clinical studies have shown that currently available therapies for MHE patients, including lactulose, probiotics, synbiotics, rifaximin, and fecal microbiota transplantation (FMT), improve cognitive dysfunction through the modulation of gut microbiota dysbiosis[14-17].

Although several published reviews have elucidated the involvement of gut microbiota dysbiosis in the pathogenesis and treatment of HE, no specific review has focused on this involvement in MHE[13,18-20]. Therefore, this review aimed to comprehensively elucidate the roles of gut microbiota in MHE pathogenesis *via* the gut-liver-brain axis and systematically analyze the underlying mechanisms linked with microbiome therapies to modulate gut microbiota dysbiosis in cirrhotic patients with MHE.

GUT MICROBIOTA DYSBIOSIS IN MHE

Small intestinal bacterial overgrowth (SIBO) is a pathological dysregulation of gut microbiota, characterized by excessive bacteria and/or abnormal bacterial composition in the small intestine. Approximately 48% to 73% of cirrhotic patients have SIBO[21]. Intestinal immune dysfunction, intestinal dysmotility, and decreased bile acid synthesis are implicated in the pathogenesis of SIBO[22]. SIBO is closely associated with the severity of advanced liver cirrhosis, and it has been validated as a significant risk factor for MHE[23,24]. In MHE patients, the gut microbiota dysbiosis resulting from the SIBO has been characterized by lower bacterial diversity, decreased autochthonous beneficial bacteria, and increased pathogenic Gram-negative bacteria[8,14,25]. The gut microbiota dysbiosis in cirrhotic patients with MHE is summarized in Table 1. Notably, Bajaj *et al*[26] found that MHE patients have higher abundances of *Enterococcus* and *Veillonella* and a lower abundance of *Roseburia* in the gut mucosal microbiota; these signatures are significantly different from those of the fecal microbiota. It is hypothesized that the adherence and overgrowth of pathogenic bacteria in the gut mucosal microbiota, rather than the fecal microbiota, might be implicated in the pathogenesis of bacterial translocation.

Table 1 Clinical studies of gut microbiota dysbiosis in cirrhotic patients with minimal hepatic encephalopathy

Ref.	Nationality	Number of patients	Etiology of cirrhosis	MHE diagnosis	Sample	Method	Microbiota alteration
Zhang *et al*[8]	China	51	AIH, HBV, PBC, alcohol	NCT-A DST	Stool	16S rRNA pyrosequencing	Enriched *Streptococcus salivarius*
Wang *et al*[14]	China	98	HBV, HCV, others	NCT-A DST	Stool	16S rRNA sequencing	Enriched *Proteobacteria*, especially *Pasteurellaceae Haemophilus* and *Alcaligenaceae Parasutterella*
Luo *et al* [29]	China	143	HBV	PHES	Stool	16S rRNA sequencing	Enriched *Streptococcus salivarius* and *Veillonella*
Liu *et al* [76]	China	55	HBV, HCV, alcohol, others	NCT-A BAEP	Stool	Stool bacterial culture	Overgrowth of *E. coli* and *Staphylococcus* spp.
Bajaj *et al* [27]	United States	97	HCV, alcohol, NASH, others	ICT PHES	Stool	Shotgun metagenomic sequencing	*Alistipes ihumii*, *Prevotella copri*, and *Eubacterium* spp. were higher, while *Enterococcus* spp. were uniquely lower in MHE diagnosed by ICT
Bajaj *et al* [28]	United States	247	HCV, alcohol, NASH, others	PHES ICT Stroop	Stool	Multi-tagged sequencing	Enriched *Lactobacillaceae*

AIH: Autoimmune hepatitis; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PBC: Primary biliary cirrhosis; NASH: Non-alcoholic steatohepatitis; NCT-A: Number connection test-A; DST: Digit symbol test; ICT: Inhibitory control test; PHES: Psychometric hepatic encephalopathy score; MHE: Minimal hepatic encephalopathy.

Because of the lack of uniform criteria for diagnosing MHE, the results of the currently available diagnostic methods for MHE are inconsistent in clinical practice. Specific signatures of fecal microbiota correspond to unique cognitive impairments determined by different diagnostic methods for MHE, including the psychometric hepatic encephalopathy score, inhibitory control test, and EncephalApp Stroop test (Table 1). For example, the abundances of *Enterococcus* and *Streptococcus* were higher in cirrhotic patients with MHE diagnosed by the psychometric hepatic encephalopathy score only; however, the abundances of *Prevotella copri*, *Eggerthela*, and *Alistipes* spp. were higher in those with MHE diagnosed by the inhibitory control test only[27]. Of note, the *Lactobacillaceae* abundance was also higher in fecal samples of MHE patients, regardless of MHE testing; therefore, this might be able to be used as a substitution for MHE testing[28].

Gut microbiota signatures of MHE patients vary depending on the etiology of liver cirrhosis. In a Chinese cohort with cirrhosis, the abundances of *Streptococcaceae* and *Veillonellaceae* were overrepresented in cirrhotic patients, and MHE patients had a higher abundance of *Streptococcus salivarius*[8]. Moreover, *Streptococcus salivarius* was also enriched in the gut microbiome of patients with MHE due to hepatitis B-associated liver cirrhosis, especially in those with sleep disturbances[29]. In contrast, in a cohort with cirrhosis in the United States, the fecal *Lactobacillaceae* abundance was higher in MHE patients; however, the abundance of fecal *Lachnospiraceae* genera, such as *Clostridium XIVb* and *Ruminococcus*, was correlated with better cognitive function independent of clinical variables[28]. Additionally, another study in the United States revealed that a higher *Veillonellaceae* abundance was found in the fecal microbiota of MHE patients, and that *Porphyromonadaceae* and *Alcaligeneceae* were positively associated with cognitive dysfunction in MHE[30]. The altered gut microbiota in Chinese MHE patients differs from that of MHE patients in the United States because the primary etiology of liver cirrhosis in the Chinese population is hepatitis B; however, in the United States, hepatitis C and excessive alcohol consumption are the predominant etiologies[31,32].

GUT-LIVER-BRAIN AXIS IN MHE

Bacterial translocation

In healthy individuals, the characteristic structure and immune system of the intestinal mucosa can prevent bacteria and their byproducts from entering the systemic circulation. In patients with liver cirrhosis, the SIBO decreases the synthesis of secondary bile acids by inhibiting the activation of Farnesoid X receptor and Takeda G protein-coupled receptor, which reduces intestinal immunoglobulin A levels and further compromises the immune function of the intestinal mucosa[33,34]. Moreover, the SIBO induces decreased synthesis of antimicrobial peptide and activates mucosal immune responses, resulting in intestinal inflammation and impaired intestinal epithelium integrity[35]. Furthermore, the SIBO increases the permeability of epithelial intercellular junctions *via* the down-regulation of tight junction protein expressions[36]. These potential mechanisms induce a “leaky gut” which facilitates the

transfer of pathogenic bacteria and their metabolites from the intestinal tract to the circulatory system, resulting in systemic inflammation (Figure 1).

Systemic inflammation

Translocated bacteria and their products, such as pathogen-associated molecular patterns, are transported to the liver through the portal vein. At the molecular level, pathogen-associated molecular patterns are recognized by Toll-like receptors and cytoplasmic nucleotide-binding oligomerization domain-like receptors, and primarily stimulate hepatic Kupffer cells through the activation of MyD88-dependent and NF-κB signaling pathways[37,38]. Innate immune responses in the liver are triggered, resulting in liver damage, with the release of damage-associated molecular patterns and the production of proinflammatory cytokines and chemokines (Figure 1)[37,38]. MHE patients present the systemic proinflammatory environment reflected by increased circulatory levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukins (ILs), and interferon, and chemokines such as CCL20, CXCL13 and CX3CL1[39].

In experimental mice with MHE, higher abundances of *Staphylococcaceae*, *Enterobacteriaceae*, and *Lactobacillaceae* in the large intestine and of *Staphylococcaceae*, *Streptococcaceae*, and *Enterobacteriaceae* in the small intestine were associated with systemic inflammation along with higher circulating concentrations of TNF-α and IL-1β[10]. Similarly, the abundances of *Enterobacteriaceae*, *Fusobacteriaceae*, and *Veillonellaceae* were positively associated with higher serum concentrations of IL-2, IL-13, and IL-23 in cirrhotic patients with MHE, and these increased cytokines were significantly correlated with MHE severity[30]. Furthermore, the association between MHE severity and increased proinflammatory cytokines has been demonstrated to be independent of the severity of liver cirrhosis and ammonia levels, suggesting that systemic inflammation with its proinflammatory cytokines is potentially implicated in the development of MHE[40].

Blood-brain barrier permeability

The blood-brain barrier is composed of capillary endothelial cells surrounded by capillary basement membrane and astrocytic perivascular endfeet. The BBB separates the systemic circulation and brain, prevents the entry of potentially harmful substances into the brain, and maintains the homeostasis of the brain microenvironment. Circulating proinflammatory cytokines cannot directly cross the BBB and exert their effects on the brain. However, these cytokines, including TNF-α, ILs, and interferon, down-regulate the expression of endothelial tight junction proteins, compromise cerebrovascular endothelial cells, activate astrocytes to an inflammatory reactive state, and alter BBB receptor expression and transport pathways, which consequently impair BBB integrity and further increase BBB permeability (Figure 2)[41,42]. Through the aforementioned mechanisms, the proinflammatory signaling, which is initiated by systemic inflammation, crosses the damaged BBB and underlies the neuroinflammatory response that develops in the cerebrum.

Neuroinflammation

Neuroinflammation refers to a series of inflammatory response processes characterized by microglial activation and proinflammatory cytokine production in the cerebrum[43]. The proinflammatory signaling, originating from systemic inflammation and crossing the BBB, induces microglial activation, stimulates Toll-like receptors, and activates NF-κB and myeloid protein-dependent pathways to produce proinflammatory mediators in the cerebrum[41]. Neuroinflammation interferes with neurotransmission, affects neuronal function, and induces low-grade cerebral edema in concert with hyperammonemia (Figure 2)[43]. Balzano *et al*[44] found that MHE rats experienced not only increased serum levels of prostaglandin E2, IL-6, and IL-17 but also microglial activation with increased mRNA expression of TNF-α and IL-1β in the hippocampus, which indicated the existence of both systemic inflammation and neuroinflammation in MHE. Additionally, *Enterobacteriaceae* in the cecum and *Staphylococcaceae* in the small intestine are linked to serum proinflammatory cytokines and neuroinflammation in cirrhotic mice[10]. Moreover, germ-free mice colonized with feces from MHE patients containing high abundances of *Enterobacteriaceae*, *Staphylococcaceae*, and *Streptococcaceae* had remarkable microglial activation and neuroinflammation[9]. Therefore, neuroinflammation is closely associated with gut microbiota dysbiosis in experimental animal models of MHE.

In contrast, the neuroinflammation in MHE patients has not been extensively studied. Postmortem examination of cerebral specimens from MHE patients showed that mRNA expressions of TNF-α, IL-1β, and IL-6 remained unchanged in the cerebral cortex, although genes related to microglial activation were upregulated[45,46]. Current evidence of the involvement of gut microbiota dysbiosis in the pathogenesis of neuroinflammation has been derived from experimental animal models of MHE; however, related studies of MHE patients are lacking. Magnetic resonance imaging (MRI) has been successfully used to quantify the manganese deposition in the brain and noradrenaline in MHE rats[47,48]. It is presumed that cerebral MRI examinations of MHE patients could facilitate further research concerning the involvement of gut microbiota dysbiosis in the pathogenesis of neuroinflammation.

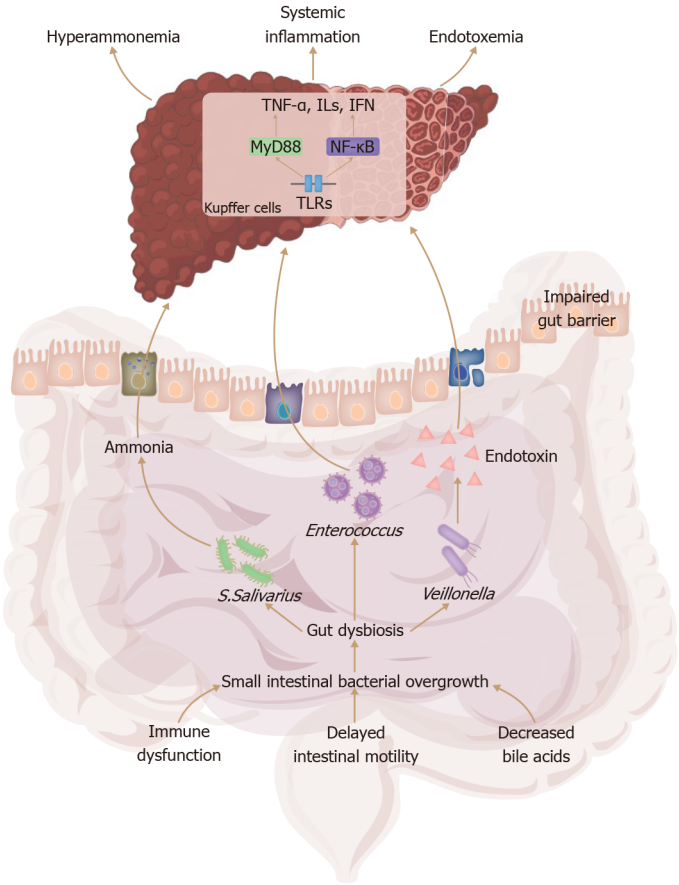

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Figure 1 On the background of liver cirrhosis with hepatic dysfunction, dysbiotic gut microbiota and its byproducts including ammonia and endotoxin cross the impaired intestinal barrier, stimulate innate immune responses in the liver, and lead to systemic inflammation, hyperammonemia, and endotoxemia. TNF-α: Tumor necrosis factor-alpha; ILs: Interleukins; IFN: Interferon.

Hyperammonemia

Ammonia, an important causative agent of MHE, is predominantly derived from the degradation of amino acids and urea by the gut bacteria. Urea hydrolysis is catalyzed by urease, an enzyme mainly produced by Gram-negative *Enterobacteriaceae*[49]. In MHE patients, an increased abundance of *Streptococcus salivarius* is associated with hyperammonemia because *Streptococcus salivarius* has a considerable number of urea catabolite genes that activate urease activity, facilitating ammonia production and accumulation, leading to further hyperammonemia[8,29,50]. *Streptococcus salivarius* might be a potential therapeutic target for ammonia-lowering strategies in MHE patients.

Hyperammonemia induces a leaky BBB, promotes glutamine accumulation in astrocytes, and leads to astrocyte swelling and subsequent low-grade cerebral edema that influences neurotransmission (Figure 2)[51,52]. Similar to systemic inflammation, chronic hyperammonemia induces microglial activation with the increased production of TNF-α, IL-1β, and IL-6 and impaired glutamatergic and GABAergic neurotransmission, resulting in cognitive deficits in MHE rats[53,54]. Moreover, treating MHE rats with anti-TNF-α, which does not cross the BBB, attenuated systemic inflammation, alleviated hyperammonemia-induced neuroinflammation, and ameliorated neurotransmission and cognitive function[44]. Experimental animal evidence indicated that hyperammonemia might be exerted in concert with systemic inflammation to drive the development of neuroinflammation.

Endotoxemia

Endotoxins, also known as lipopolysaccharides, are components of the outer membrane of Gram-negative bacteria. In patients with liver cirrhosis, serum endotoxin levels are increased and correlated with MHE severity, and functional modules associated with endotoxin production are abundant in the gut microbiome of MHE patients[11,29]. Several studies reported that increased endotoxin production was related to a higher *Veillonella* abundance in MHE patients[55,56]. Due to the impaired intestinal barrier and portal-systemic shunting, endotoxins enter the systemic circulation and cause endotoxemia with increased production of pro-inflammatory cytokines (Figure 1)[57]. Similar to pro-inflammatory cytokines, endotoxin is also unable to cross the BBB. Nevertheless, endotoxin stimulates microglia to release TNF-α, IL-1β, and reactive oxygen species, which increases the permeability of BBB tight

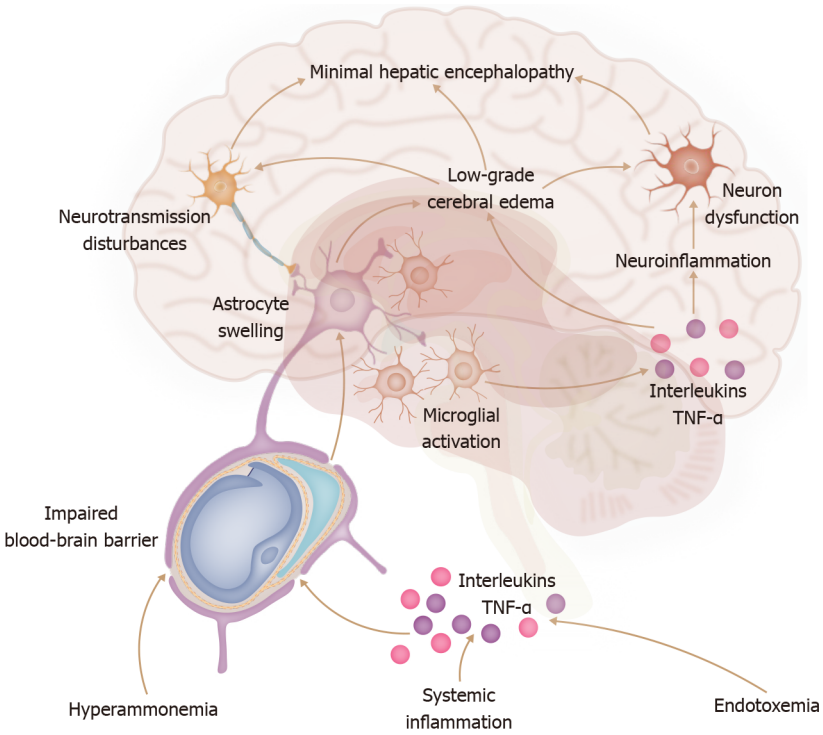

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Figure 2 Systemic inflammation, hyperammonemia, and endotoxemia influence the permeability of the blood-brain barrier, resulting in neuroinflammation and low-grade cerebral edema, contributing to the pathogenesis of minimal hepatic encephalopathy. TNF-α: Tumor necrosis factor-alpha.

junctions[58]. Peripheral lipopolysaccharide injection induces microglial hyperactivation, increases mRNA expressions of TNF-α, IL-1β, and IL-10 in the cerebral cortex, and impairs glutamate transmission, resulting in memory and learning deficits in mice[59,60]. Based on the synergistic effect of hyperammonemia, peripheral lipopolysaccharide injection induced cytotoxic brain swelling and a subsequent pre-coma status in cirrhotic rats[61]. However, the exact mechanism of the interaction between hyperammonemia and endotoxemia in the pathogenesis of MHE remains unclear and requires further research.

MICROBIOME THERAPEUTICS FOR MHE

The majority of current therapeutic strategies for MHE in clinical practice exert their effects through modulation of gut microbiota dysbiosis. These microbiome therapies, including lactulose, rifaximin, probiotics, synbiotics, and FMT, alter the composition and function of the gut microbiota, inhibit pathogenic bacterial overgrowth, increase the abundance of beneficial bacteria, and reduce the production and absorption of ammonia (Table 2).

Lactulose

Lactulose, the standard therapy for MHE, is considered a prebiotic. A multicenter, randomized, controlled trial in China suggested that lactulose reduces ammonia production and absorption by inhibiting the growth of ammonia-producing bacteria, such as *Streptococcus salivarius*, and facilitates the growth of beneficial saccharolytic bacteria, such as *Bifidobacterium* and *Lactobacillus*[14]. Moreover, several studies have revealed that lactulose reduces the serum concentrations of TNF-α, ILs, and endotoxins by inhibiting SIBO and bacterial translocation, thus improving cognitive dysfunction of MHE patients[11,62,63].

Despite lactulose treatment for MHE patients, there was still an increased gut microbiota dysbiosis with a lower cirrhosis dysbiosis ratio and enriched Gram-negative bacteria such as *Enterobacteriaceae* and *Bacteroidaceae*[64]. Similarly, Sarangi *et al*[65] indicated that lactulose did not significantly influence bacterial diversity, species richness, or taxa abundance in the gut microbiome of cirrhotic patients with MHE. Moreover, lactulose withdrawal only decreased the *Faecalibacterium* abundance and did not remarkably alter the gut microbiota composition[24]. These studies suggest that alterations in the gut microbiota function, rather than changes in the gut microbiota composition, may be associated with the therapeutic effects of lactulose in MHE patients.

Table 2 Clinical Studies of gut microbiota modulation in cirrhotic patients with minimal hepatic encephalopathy

Ref.	Design	Patients	Duration	Sample	Method	Microbiota alteration	Therapeutic effect
Lactulose							
Wang *et al* [14]	Multi-centre, open-label, randomized controlled trial	lactulose (n = 67), control (n = 31)	60 d	Stool	16S rRNA sequencing	Higher abundances of *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria* were in non-responders for lactulose	Significantly ameliorated MHE
Rifaximin							
Bajaj *et al* [56]	Controlled clinical trial	MHE patients before/after rifaximin (n = 20)	8 wk	Stool	Multi-tagged pyrosequencing, GC/LC-MS	Modest decrease in *Veillonellaceae* and increase in *Eubacteriaceae*, with significant changes in metabolite correlations	Significant improvement in endotoxemia and cognition
Probiotics							
Lactobacillus GG							
Bajaj *et al* [74]	Randomized phase I, placebo-controlled trial	Probiotic (n = 14), placebo (n = 16)	8 wk	Stool	Multi-tagged pyrosequencing, GC/LC-MS	Decreased *Enterobacteriaceae* and increased *Lachnospiraceae* and *Clostridiales Incertae Sedis* XIV, with significant alterations in metabolite correlations with amino acid and secondary bile acid metabolism	Attenuated endotoxemia and decreased TNF-α without change in cognition
Probiotics							
Clostridium butyricum combined with *Bifidobacterium infantis*							
Xia *et al* [73]	Randomized controlled trial	Probiotic (n = 30), placebo (n = 37)	3 mo	Stool	16S rRNA sequencing	Increased *Clostridium cluster* I and *Bifidobacterium*, decreased *Enterobacteriaceae* and *Enterococcus*	Reduced ammonia and improved cognition
Escherichia coli Nissle 1917 strain							
Manzhalii *et al*[75]	Single-centre, open-label, randomized trial	Probiotic (n = 15), lactulose (n = 15), rifaximin (n = 15)	1 mo	Stool	16S rRNA sequencing	Normalized *Bifidobacterium* and *Lactobacilli* abundance	Reduced ammonia and pro-inflammatory cytokines and improved cognition
Rifaximin plus probiotic							
Zuo *et al* [84]	Controlled clinical trial	Rifaximin (n = 7), rifaximin plus probiotic (n = 7)	4 wk	Stool	16S rRNA sequencing	Both treatments alone reduced the overall microbiome diversity, with decreased *Streptococcus* and *Faecalibacterium*, *Clostridium* and increased *Lactobacillus*	Rifaximin plus probiotics showed a more apparent effect
Rifaximin plus lactulose							
Schulz *et al*[72]	Randomized controlled trial	Rifaximin (n = 1), rifaximin plus lactulose (n = 4)	3 mo	Stool	16S rRNA sequencing	Rifaximin with or without lactulose did not affect microbiota composition	MHE improvement with rifaximin lasted after the end of treatment
Synbiotics							
Probiotics plus fermentable fiber							
Liu *et al* [76]	Controlled clinical trial	Synbiotic (n = 20), fermentable fiber (n = 20), placebo (n = 15)	30 d	Stool	Stool quantitative bacteriological culture	Significant increase in non-urease-producing *Lactobacillus* species	Reduced ammonia and endotoxemia levels, reversal in 50% of MHE patients

GC/LC-MS: Gas chromatography/liquid chromatography-mass spectrometry; TNF-α: Tumor necrosis factor-alpha; MHE: Minimal hepatic encephalopathy.

Rifaximin

Rifaximin is an oral semisynthetic and nonsystemic antibiotic that inhibits transcription and RNA synthesis by binding to the β-subunit of bacterial RNA polymerase, with lower gastrointestinal absorption and better antimicrobial activity[66]. As an antibiotic, rifaximin also reduced pro-inflammatory cytokines and attenuated systemic and intestinal inflammation in a mouse model of MHE[10]. Similarly, rifaximin-α inhibited serum neutrophil TLR-4 expression, decreased TNF-α and IL levels, and ameliorated MHE in cirrhotic patients[67].

A systematic review and meta-analysis showed that rifaximin is an effective and safe therapy for SIBO with a higher overall eradication rate[68]. In a mouse model of MHE, rifaximin therapy decreased intestinal ammonia production and serum IL-1β and IL-6 Levels by altering the gut microbiota function with increased secondary bile acids and decreased deconjugation without altering the gut microbiota composition[69]. Similarly, several clinical studies revealed that rifaximin attenuated hyperammonemia and endotoxemia in patients with MHE and resulted in significant changes in gut metabolites with modest alterations in gut microbiota composition, such as decreased *Streptococcus* and *Veillonella* abundance[56,70,71]. Furthermore, long-term treatment with rifaximin with or without lactulose did not affect the gut microbiota composition over a period of 3 mo in cirrhotic patients with MHE[72]. The results of these studies further support the theory that rifaximin treats MHE by modulating the metabolic function of the gut microbiota rather than gut microbiota composition, similar to the mechanism of lactulose treatment for MHE.

Probiotics

Probiotics, which are added to yogurt or consumed as food supplements, are live bacteria with various health benefits. Treatment with probiotics containing *B. infantis* and *C. butyricum* increased *Bifidobacterium* and *Clostridium cluster* I abundances and decreased *Enterococcus* and *Enterobacteriaceae* abundances, thereby significantly lowering serum ammonia levels of patients with hepatitis B-associated liver cirrhosis[73]. Additionally, the probiotic *Lactobacillus* GG increased *Clostridiales* XIV and *Lachnospiraceae* abundances, decreased the *Enterobacteriaceae* abundance, and decreased serum endotoxemia and TNF-α levels, resulting in alterations in metabolites associated with amino acid and secondary bile acid metabolism[74]. Moreover, the probiotic *Escherichia coli Nissle* strain reduced the levels of ammonia and pro-inflammatory cytokines, normalized *Lactobacilli* and *Bifidobacterium* abundances, and improved the cognitive function of MHE patients[75]. A systematic review of 19 trials showed that probiotics increased beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, decreased SIBO and endotoxemia, and reversed MHE without affecting systemic inflammation[15]. Compared with other modalities, including lactulose, rifaximin, and L-ornithine-aspartate, probiotics have similar therapeutic effects on MHE reversal and OHE prevention, and no significant differences were observed in the gut microbiota composition when probiotics and lactulose were compared[15,73]. Probiotics are regarded as alternative therapies for MHE. In contrast to lactulose and rifaximin, probiotics have therapeutic effects on MHE by altering the gut microbiota composition. Because of the complicated interconnections within the gut microbiome, a single change in the gut microbiota composition may have an unexpected effect or no effect at all. The interactions among supplemental probiotics, autochthonous beneficial bacteria, and pathogenic bacteria in the intestinal tract remain to be determined.

Synbiotics

Synbiotics are a combination of probiotics and prebiotics. It is hypothesized that synbiotics improve the effectiveness of probiotics in the human intestine. A synbiotic containing probiotics and fermentable fibers significantly increased the nonurease-producing *Lactobacillus* abundance, decreased serum ammonia levels, and reversed MHE in cirrhotic patients[76]. Moreover, a combination of *Bifidobacterium longum* and fructo-oligosaccharide, which is another symbiotic, decreased serum ammonia levels and improved the cognitive function of MHE patients[77]. A systematic review revealed that synbiotic supplementation decreased SIBO, increased beneficial commensal bacteria such as *Lactobacillus* and *Bifidobacterium*, reduced blood ammonia and endotoxin levels, and decreased the risk of MHE recurrence[15]. Both a synbiotic and a prebiotic alone reduced ammonia and endotoxin levels, decreased the fecal *Escherichia coli* abundance, and reversed MHE; however, the synbiotic did not show better efficacy than the prebiotic alone[76]. Compared with prebiotics and probiotics used alone, the clinical benefits of synbiotics have yet to be demonstrated.

Fecal microbiota transplantation

FMT refers to the process of transferring fecal bacteria from healthy donors to patients with gut microbiota dysbiosis[78]. FMT is an effective therapy for *Clostridioides difficile* infection and inflammatory bowel diseases[78,79]. In germ-free mice colonized with feces from MHE patients, FMT modulated gut microbiota dysbiosis and ameliorated microglial activation and neuroinflammation independent of active liver inflammation[9]. In cirrhotic patients with MHE, oral FMT capsules increased *Ruminococcaceae* and *Bifidobacteriaceae* abundances, decreased *Streptococcaceae* and *Veillonellaceae* abundances, and reduced serum IL-6 and lipopolysaccharide-binding protein[17]. Furthermore, long-term treatment with FMT increased *Burkholderiaceae* abundance and decreased *Acidaminoccocaceae* abundance, which prevented HE recurrence and improved cognitive function during the follow-up[80]. The role of FMT in preventing OHE recurrence by modulating gut microbiota dysbiosis has been demonstrated; however, no clinical trial regarding the FMT for MHE treatment has been reported so far. It could be presumed that FMT is a potential and effective microbiome therapy for MHE; this would require rigorous clinical trials for verification.

Clinical studies of FMT for MHE have used different routes, doses, and dosing times. Owing to these differences, uniform criteria for selecting ideal FMT donors are lacking, and the optimal FMT dosing

regimen remains unclear. Moreover, the identification of pathogens in FMT donors is difficult. FMT is associated with Shigatoxin-producing *Escherichia coli*, extended-spectrum-β-lactamase-producing *Escherichia coli*, and enteropathogenic *Escherichia coli* infections due to the lack of donor screening[81,82]. Patients with liver cirrhosis are vulnerable to infection because of their weakened immune systems; therefore, rigorous screening and selection of FMT donors would improve FMT safety for patients with MHE.

Challenges and controversies

One major challenge of microbiome therapies for MHE is that host factors, dietary habits, and long-term medications may influence the gut microbiome of MHE. *Ruminococcus gnavus* and *Streptococcus salivarius* were the predictors of response to rifaximin treatment, and a higher abundance of *Bacteroidetes*, *Firmicutes*, *Actinobacteria,* and *Proteobacteria* could predict poor response to lactulose treatment[14,83]. Moreover, patients with MHE caused by non-alcoholic cirrhosis responded better to the treatment with rifaximin plus probiotics because they presented a significant decrease in ammonia-producing bacteria genera, such as *Clostridium* and *Streptococcus*[84]. Before the microbiome therapies, the baseline signatures of gut microbiota are identified to match the appropriate microbiome therapies, and gut microbiota biomarkers are explored to predict the therapeutic effects. Based on the different baseline compositions of gut microbiota, targeted and personalized microbiome therapies might be potentially effective strategies for MHE treatment.

Furthermore, cirrhosis is a chronic liver disease, and gut microbiota dysbiosis caused by liver cirrhosis may persist for a long time and require maintenance treatment. However, most microbiome therapeutics are currently single and short-term therapies. After probiotic yogurt supplementation for more than 2 mo, patients with liver cirrhosis had significant MHE reversal rates and excellent compliance; moreover, the potential for long-term compliance existed[85]. Additionally, MHE amelioration with rifaximin treatment for more than 3 mo lasted after the end of treatment, thus indicating a long-term effect on the metabolic function of the gut microbiota[72]. The efficacy and safety of long-term microbiome therapies for MHE require multicenter studies with large populations.

Another related challenge is that rifaximin, a validated antibiotic for MHE, potentially increases antibiotic resistance in liver cirrhosis. A large European cohort study of patients with liver cirrhosis revealed a significant increase in the prevalence of multidrug-resistant bacteria from 29% to 38% during the past decade[86]. Moreover, Chang *et al*[87] reported that rifampin-resistant *staphylococcal* isolates appeared after rifaximin treatment and disappeared during the short term in cirrhotic patients. Prophylactic use of rifaximin did not alter the diversity and composition of gut microbiota or the overall resistance over 12 wk[88]. Rifaximin has not induced significant bacterial resistance and has shown active antimicrobial activity against most bacteria. Multi-drug resistant bacteria should be monitored when using rifaximin in MHE patients, especially in cirrhotic patients previously treated with antibiotics.

CONCLUSION

Gut microbiota dysbiosis initiates the pathophysiological mechanisms of hyperammonemia, systemic inflammation, and endotoxemia, which contribute to neuroinflammation *via* the gut-liver-brain axis in MHE. Currently available strategies for MHE treatment mainly involve the modulation of gut microbiota dysbiosis. In the future, based on the specific microbial signatures identified, personalized and targeted microbiome therapies with optimal regimens and doses may improve the efficacy and safety of MHE treatments.

FOOTNOTES

Author contributions: Luo M and Xin RJ designed the outline, prepared the tables, and drafted the manuscript; Hu FR and Yao L summarized the data and plotted the figure; Hu SJ and Bai FH revised the manuscript. All authors approved the final version of the manuscript.

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