REVIEW ARTICLES

e-ISSN 1643-3750
© Med Sci Monit, 2025; 31: e949286
DOI: 10.12659/MSM.949286

Received: 2025.04.07
Accepted: 2025.08.19
Available online: 2025.09.17
Published: 2025.11.09

A Review of Recent Advances in Fecal Microbiota Transplantation for the Treatment of Hepatic Encephalopathy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Junru Fang
ABCDEFG 2 Jian Fang

1 Department of Gastroenterology, The First Affiliated Hospital of Henan University, Kaifeng, Henan, PR China
2 Department of Neurology, The Second People's Hospital of Longgang District, Shenzhen, Guangdong, PR China

Corresponding Author: Jian Fang, e-mail: Fjdoctorfj@163.com
Financial support: Supported by Henan Medical Science and Technology Research Project (LH-GJ20210555)
Conflict of interest: None declared

Hepatic encephalopathy (HE) results from a debilitating complication of liver cirrhosis and acute liver failure, characterized by neuropsychiatric abnormalities ranging broadly from mild cognitive impairment to respiratory failure to coma. The pathogenesis of HE is multifactorial, with gut-derived toxins, particularly ammonia, playing a central role. Recent advances in understanding the gut-liver-brain axis have revealed the importance of gut microbiota and dysbiosis in the development and progression of HE. Fecal microbiota transplantation (FMT), a clinical procedure that is performed to transfer fecal microbiota from a healthy donor to a patient with HE (recipient), has emerged as a promising therapeutic strategy for modulating gut microbiota and ameliorating HE. FMT facilitates the restoration of gut microbiota composition with increased microbial alpha diversity, reestablishment of the balance between beneficial and pathogenic bacteria, reduction in the production of gut-derived toxins, and improvement of intestinal barrier function. It also modulates immune and inflammatory responses, alleviating hepatocyte and biliary injury. FMT has also demonstrated efficacy in improving cognitive function and reducing hospitalizations in HE patients and can maintain a stable donor-like microbiota profile for up to 12 months post-transplantation. FMT is generally well-tolerated, with most adverse events reported to be mild and transient, providing a desirable option for HE treatment. This review provides a comprehensive overview of the current understanding of the role of gut microbiota in the pathogenesis of HE, the mechanisms underlying the therapeutic effects of FMT, and the clinical evidence supporting its use in HE. We will also discuss the limitations, challenges, and future prospects for FMT in the treatment of HE.

Keywords: Fecal Microbiota Transplantation • Liver Cirrhosis, Alcoholic • Encephalopathy, Bovine Spongiform • Liver Failure • Ammonia

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/949286

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Introduction

Hepatic encephalopathy (HE) is a severe complication of cirrhosis that presents as a complex neuropsychiatric syndrome in patients with liver dysfunction [1,2]. In severe cases, it can lead to coma, respiratory failure, and even death [3]. Based on the etiology, HE is usually attributed to acute liver failure, portal systemic shunt, and liver cirrhosis [4]. Overt HE is the most severe form of HE, and is characterized by alteration of consciousness or coma. The prevalence of overt HE ranges from 30% to 45%, whereas the prevalence of minimal HE, a pervasive frequent complication of cirrhosis of any etiology, may be as high as 85% [5]. Therefore, HE imposes a substantial burden on healthcare systems worldwide [6] and has a negative impact on the quality of life of the patient [3]. The gut-liver-brain axis is a bidirectional communication system linking the gut microbiota, liver, and brain [7]. In patients with cirrhosis, the composition of gut microbiota is often altered, resulting in an overgrowth of pathogenic bacteria and a reduction in beneficial bacteria. Consequently, dysbiosis can lead to increased production of gut-derived toxic metabolites, such as ammonia, which can transmit across the blood-brain barrier and contribute to the neuropsychiatric symptoms associated with HE [8]. Furthermore, gut dysbiosis can lead to systemic inflammation and oxidative stress, further exacerbating liver injury and contributing to the progression of HE [9].

The pathogenesis of HE has not been fully elucidated, but it is widely accepted that gut-generated toxins, particularly ammonia, play a central role [10,11]. Hyperammonemia and inflammation, oxidative stress, and neurotransmitter dysfunction are involved in the disease [12]. At present, antibiotics, lactulose, and lactitol targeting the gut microbiota are the first-line therapy for treating HE. However, drug interventions have significant gastrointestinal adverse reactions and are ineffective in approximately 20% of patients with chronic liver failure and HE [13,14]. For these patients, alternative treatment options, such as emerging therapies like fecal microbiota transplantation (FMT) are needed. FMT is a clinical procedure to transfer fecal microbiota from a healthy donor to a patient with HE (recipient) to restore a healthy gut microbiota composition in the recipient [15]. FMT has been successfully used to treat recurrent infection of *Clostridioides difficile* and is being investigated for a variety of other conditions and diseases [16,17]. Given the critical role of gut microbiota in the pathogenesis of HE, FMT has emerged as a promising therapeutic and management strategy for this condition [18-20], and has shown promise in modulating the gut microbiota to reduce the production of gut-bacteria-derived toxins. Several preclinical studies have demonstrated the beneficial effects of FMT in animal models of HE. For example, a study by Kang et al showed that FMT significantly reduced ammonia levels and enhanced cognitive function in a rat model of HE [21]. Similarly, Bajaj et al found that FMT accelerated the recovery of impaired cognitive function due to HE and reduced systemic inflammation in patients with cirrhosis and minimal HE [19] (**Table 1**).

Despite the promising and positive results from preclinical and clinical studies, there are several challenges that need to be addressed before FMT can be widely adopted as a routine treatment for HE. One of the main challenges is the lack of standardized clinical protocols for FMT that specify donor selection, preparation of fecal materials, and administration routes. Currently, FMT is typically administered via colonoscopy, nasoenteric tube, or oral capsules, but the optimal route of administration for HE remains unclear and may vary among patients [22,23]. Another challenge is the potential risk of adverse events, including infections and immune reactions, which need to be carefully monitored and managed [24]. While early studies have shown promising results, the sample sizes have been relatively small, and the follow-up periods have been relatively short. Larger, randomized controlled trials with longer follow-up periods are needed to confirm the benefits of FMT and to identify the patient groups that are most likely to respond to and benefit from this treatment [25].

In this review, we aimed to provide a comprehensive overview of the current understanding on the role of gut microbiota in HE pathogenesis, the mechanisms underlying the therapeutic effects of FMT, and the clinical evidence supporting its use in HE. We will also discuss the limitations, challenges, and future prospects for FMT in the treatment of HE.

Gut Microbiota and Pathogenesis of HE

The gut microbiota make up the intestinal microbiome, a complex and dynamic ecosystem that plays an important role in maintaining host health and exerts a marked influence on the host during homeostasis and disease. A healthy microbiome is highly diverse, with approximately 1000 microbial species consisting of bacteria, viruses, fungi, and even protozoa – that colonize the human host [26]. These microbes are involved in various physiological and anti-pathogenic processes, including digestion, immune modulation, and defense against pathogens. The main populations of human gastrointestinal microorganisms include Bacteroidetes, Actinobacteria, Firmicutes, and Proteobacteria [27,28]. In healthy adults, the gut microbiota mainly consist of Bacteroidetes and Firmicutes, accounting for approximately 90% of the microorganisms in the gut that impact the physiological functions of adults. However, the abundance and diversity of microbial populations vary considerably among individuals [29]. The gut microbiome plays an important role in metabolism, immune defense, and endocrine feedback, and is strongly related to liver diseases, neurological diseases, skin diseases, and more. At present, the close association

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. The efficacy and adverse effects of fecal microbiota transplantation in the management of hepatic encephalopathy.

Study	Type	Population	Intervention	Control	Cognition	Microbiota	Liver function	Adverse effects
Philips et al [123], 2017	Pilot study	80 patients with severe hepatitis	30 grams of donor stool samples infused daily for 7 d	SOC	HE resolved in 6 out of 8 patients after FMT (71.4%)	1 yr post-FMT, there was an increase in Firmicutes and a reduction in Proteobacteria and Actinobacteria	Bilirubin levels significantly decreased	Excessive flatulence reported by 50% of FMT patients
Bajaj et al [19], 2017	RCT	20 cirrhotic patients experiencing recurrent HE	FMT enema	SOC (lactulose and rifaximin)	Significant improvement in both the PHES total score and Encephal App Stroop	Increased diversity and beneficial taxa (Lactobacillaceae and Bifidobacteriaceae) after FMT	No change	Tolerated treatment with no mental status hospitalizations
Mehta et al [100], 2018	Case series	10 patients, previously treated with FMT for recurrent HE	FMT via colonoscopy	None	Not reported	Not reported	Not reported	1 patient died due to bronchopneumonia complications
Bajaj et al [98], 2019	RCT	20 patients with cirrhosis	FMT enema	SOC	Fewer HE episodes	Increased Burkholderiaceae and decreased Acidaminococcaceae	Not reported	None reported
Bajaj et al [103], 2019	RCT	20 cirrhotic patients experiencing recurrent HE	15 FMT capsules from a single donor	Placebo	Significant improvement in Off Time + On Time	Increased duodenal mucosal diversity and reduced Streptococcaceae and Veillonellaceae	Not reported	1 HE episode
Sung et al [52], 2019	Pilot	62 patients with cirrhosis and AHE	FMT enema	None	Not assessed	Increased *Veillonella parvula*, *Clostridium cluster* XI, *Prevotella*, *Enterococcus*, *Schlegelella*, *Megasphaera*, *Lactobacillus* Decreased *Phascolarctobacterium*, *Bacteroides*, *Alistipes*	Not reported	Not reported
Bajaj et al [124], 2021	RCT	10 patients with cirrhosis and alcohol use disorder	FMT enema	Placebo	Improvements in both PHES and EncephalApp Off Time + On Time after FMT	Increased diversity, alongside elevated levels of *Odoribacter*, *Bilophila*, *Alistipes*, and *Roseburia* after FMT	No changes in AST, ALT, or albumin levels	A significant decreased SAE observed in the FMT group
Bloom et al [104], 2022	RCT	10 cirrhotic patients, previously suffered at least 1 episode of overt HE	Oral FMT capsules on days 1, 2, 7, 14, and 21	None	PHES demonstrated improvement after 3 doses of FMT	Higher *Bifidobacterium* abundance in FMT responder	Not reported	4 minor adverse effects were noted

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1 continued. The efficacy and adverse effects of fecal microbiota transplantation in the management of hepatic encephalopathy.

Study	Type	Population	Intervention	Control	Cognition	Microbiota	Liver function	Adverse effects
Li et al [78], 2022	Case series	2 patients diagnosed with liver cirrhosis	FMT using 50 g of fresh fecal intestinal flora suspension	None		Notably increased *Ruminococcus*, *Akkermansia*, and *Oscillospiraceae*, alongside decreased abundance of *Veillonella* and *Megasphaera*	Improvement in Case 1	No FMT-related adverse events or infection complications
Philips et al [125], 2022	Retrospe-ctive analysis	47 patients diagnosed with severe alcohol-associated hepatitis	100 mL of freshly processed stool introducing via nasoduodenal tube	Pentox-ifylline	Significantly lower HE incidences compared to the SOC group	Decrease in Proteobacteria and an increase in Actinobacteria and Bacteroidota	Not reported	Acute variceal bleeding was the most common cause of death in the FMT group
Bajaj et al [126], 2025	open-label pilot study	10 patients with cirrhosis and a history of overt HE	FMT capsules	Rifaximin and lactulose	Improved cognition in HE	Higher levels of *Bifidobacterium*	Not reported	Not reported

AST – aspartate aminotransferase; ALT – alanine aminotransferase; FMT – fecal microbiota transplant; HE – hepatic encephalopathy; PHES – psychometric hepatic encephalopathy score; RCT – randomized controlled trial; SAE – sepsis-associated encephalopathy; SOC – control group.

between gut microbiota and HE occurrence is being increasingly revealed and elucidated [30]. In patients with liver cirrhosis, significant changes occur in the gut microbiota, leading to a condition known as dysbiosis, in which gut microbial diversity is reduced, with an overgrowth of potentially pathogenic bacteria, and a decrease in beneficial bacteria [31,32].

Dysbiosis in patients with cirrhosis leads to increased intestinal permeability, bacterial translocation, and the production of gut-derived toxins, such as ammonia, endotoxins, and cytokines. Dysbiosis and increased intestinal permeability contribute to the translocation of bacterial products, such as lipopolysaccharides (LPS), also known as endotoxin, into the liver, triggering inflammation and insulin resistance [33]. These metabolic changes can affect brain function, leading to conditions such as depression and cognitive impairment [34]. In patients with HE, the liver's ability to detoxify these substances is impaired, resulting in toxin accumulation in the systemic circulation and subsequent neurotoxicity [10,35]. Dysbiosis can be further exacerbated as a result of small intestinal bacterial overgrowth (SIBO), increased intestinal permeability, and altered bile acid metabolism [36]. Dysbiosis not only increases toxin production but also promotes systemic inflammation, further exacerbating HE. It has been shown that gut microbiota diversity (alpha diversity) is significantly reduced in HE patients, and that this reduction is correlated with disease severity and cognitive impairment [37]. In patients with liver cirrhosis, dysbiosis and increased intestinal permeability lead to the translocation of toxin-generating bacteria and gut-derived toxins into the portal circulation. These toxins are then transported to the liver, where they contribute to liver injury and inflammation [38]. In addition, the toxins can enter the systemic circulation and cross the blood-brain barrier, leading to neuroinflammation and neurotoxicity [39].

Although the mechanism of pathogenesis of HE is not yet fully elucidated, ammonia has long been considered the primary driver of HE. Compared with patients with cirrhosis without HE, the microbiota in patients with HE contains more members of the Veillonellaceae family. A large-scale assessment indicated that the gut microbiota in patients with liver cirrhosis shows an increase in pathogenic bacteria such as *Veillonella* and *Streptococcus* [40]. Ammonia is produced by gut bacteria through the breakdown of dietary proteins and urea. In healthy individuals, ammonia waste is efficiently metabolized and detoxified in the liver through the urea cycle. However, in patients with liver cirrhosis, the urea cycle is impaired, leading to hyperammonemia. Ammonia can be transported to the brain across the blood-brain barrier and exerts neurotoxic effects by altering neurotransmitter systems, inducing oxidative stress, and causing astrocyte swelling which disturbs neuronal-glial functions [41,42]. This leads to brain edema with increased intracranial pressure and possibly death [43].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

In addition to ammonia, other gut-derived molecules, such as LPS (also known as endotoxin) and inflammatory cytokines, have been implicated in the pathogenesis of HE [44]. Endotoxin can activate the innate immune system, upregulating the release of pro-inflammatory cytokines, which can further exacerbate liver injury and neuroinflammation [45]. Recent studies suggest that microbial metabolites, such as short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), and inflammatory cytokines, also play significant roles in the pathogenesis of HE. For instance, SCFAs, while generally beneficial, can exert neurotoxic effects in the context of HE due to their interaction with the gut-brain axis [46,47]. Additionally, neuroinflammation and cognitive decline in HE patients has been attributed to TMAO, a metabolite derived from certain gut microbes [48]. In a prospective study of 49 patients with liver cirrhosis, it was found that there is a negative relationship between bacterial species producing SCFAs and the severity of cirrhosis. In patients with a history of overt HE, the concentrations of 6 specific SCFAs (acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, and succinic acid) were lower, supporting the critical role of these metabolites in preventing the pathogenesis of HE [46].

The role of inflammatory reactions and toxic substances in the pathogenesis of HE is also gradually being recognized [49]. Alterations in the structure and populations of gut microbiota and their metabolites, changes in bacterial immune response, and microbiota translocation can lead to HE by increasing the production and metabolism of ammonia and inducing the production of inflammatory mediators, thereby negatively affecting the nervous system [50]. Studies have suggested that, compared with patients with cirrhosis without cognitive impairment, patients with minimal HE and overt HE exhibit specific changes in their gut microbiota [3]. Bajaj et al demonstrated that there is a significant difference in fecal microbiota structure between patients with cirrhosis and healthy individuals [51]. Another study showed that, compared with patients with compensated cirrhosis, during the onset of acute HE, the diversity of the gut microbiome and the relative abundance of bacteroidetes decreased dramatically, while the relative abundance of Firmicutes, Proteobacteria, and Actinobacteria increased correspondingly. This suggests that overt HE-specific gut bacterial taxa may be involved in HE development, and that this phenomenon may be explored to predict clinical outcomes of HE treatments [52].

Gut-Liver-Brain Axis

The gut-liver-brain axis is a bidirectional communication network that integrates the gut, liver, and brain through neural, endocrine, immune, and metabolic pathways (**Figure 1**). It is implicated in metabolic disorders such as non-alcoholic fatty liver disease and type 2 diabetes [53,54] and involves complex interactions among the gut microbiota, the intestinal barrier, the liver, and the central nervous system [55]. Under normal physiological conditions, metabolites enter the liver through the portal vein system and are metabolized in the liver to produce bile acids and immunoglobulin. When the population of gut microbiota is imbalanced, this imbalance can lead to metabolic disorders in the liver, including loss of the ability to effectively eliminate harmful metabolic products, leading to liver diseases, such as alcoholic liver disease, fatty hepatitis, and acute and chronic liver failure [56,57]. This axis plays a critical role in maintaining homeostasis and has been implicated in various diseases, including HE, metabolic disorders, and neurodegenerative diseases. The gut microbiota play a central role in this axis by modulating the production of gut-derived toxins, regulating intestinal permeability, and influencing immune and inflammatory responses [58,59]. In liver cirrhosis, impaired liver function and portosystemic shunting lead to the accumulation of gut-derived toxins, such as ammonia, mercaptans, and endotoxins, in the bloodstream. These toxins cross the blood-brain barrier, contributing to neuroinflammation and astrocyte dysfunction, which are hallmarks of HE. Certain gut microbes play a central role in producing these toxins, particularly through the metabolism of nitrogenous compounds [60,61].

Signal transduction in the gut-liver-brain axis is also influenced by the vagus nerve, which provides a direct communication pathway between the gut and the brain. The vagus nerve can sense changes in the gut microbiota and transmit signals to the brain, leading to modulation of neuroinflammation and cognitive function. In patients with HE, vagal dysfunction may contribute to the development of neuropsychiatric symptoms [62].

FMT may restore gut-brain axis communication, improving neurological and psychiatric symptoms. Recent investigations found that FMT alleviated depression-like behaviors by modulating gut microbiota and serotonin production [63,64].

FMT Mechanisms of Action

Restoration of Healthy Gut Microbiota Composition

FMT transfers fecal microbiota from a healthy donor to a recipient (such as an HE patient) with the aim of reconstructing a healthy gut microbiome in the recipient (**Figure 2**). The donor's fecal microbiota are typically rich in beneficial bacteria, such as *Bacteroidetes* and *Firmicutes*, and have a high level of microbial diversity. In contrast, patients with HE often have a dysbiotic gut microbiome characterized by a reduction in microbial diversity and an overgrowth of potentially pathogenic microbes [65,66]. As a result of FMT, microbial alpha diversity

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

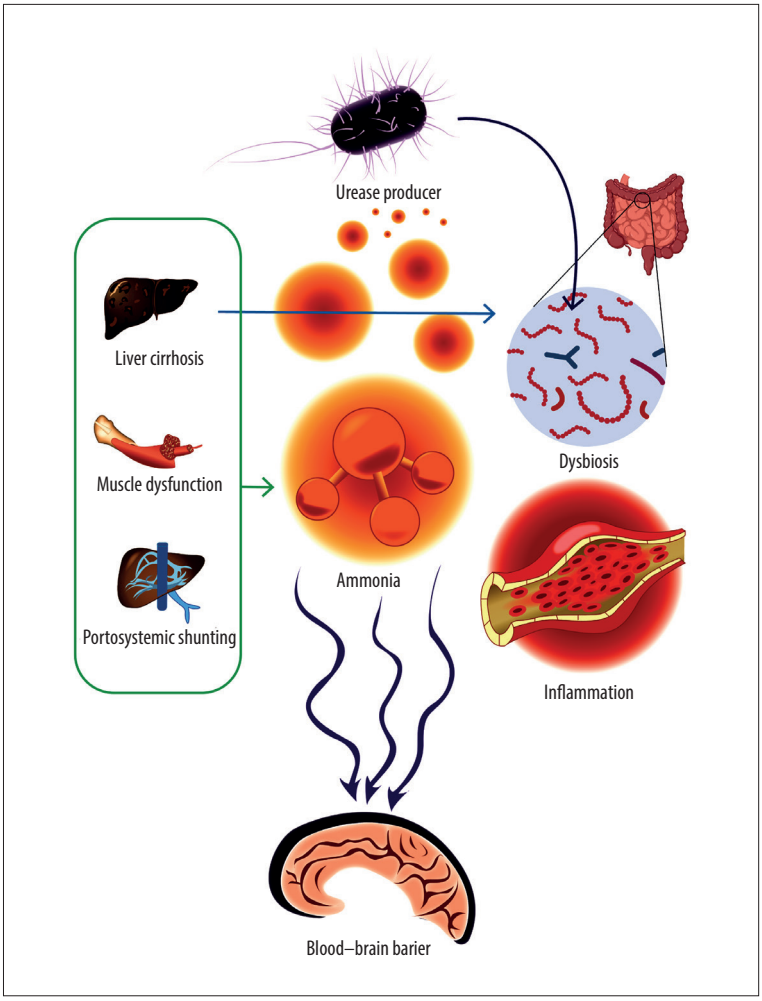

Figure 1. Gut-liver-brain axis and hepatic encephalopathy (*created with Microsoft Paint, Version 11*).

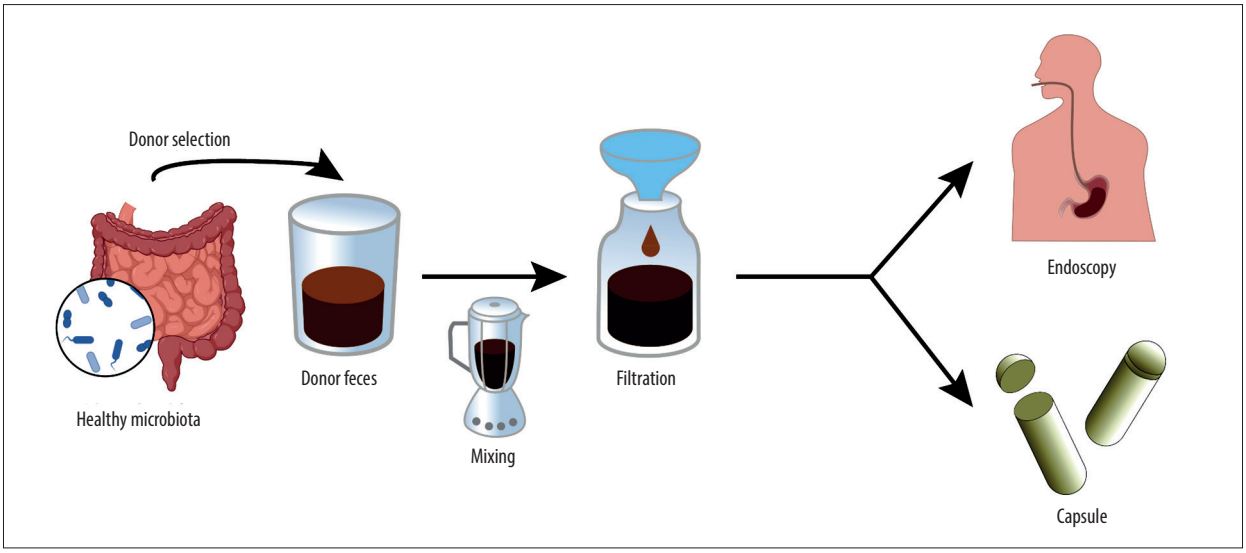

Figure 2. Procedure of fecal microbiota transplantation (*created with Microsoft Paint, Version 11*).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

in HE patients with recurrent *Clostridium difficile* infection (rCDI) was found to be significantly increased, leading to clinical improvement of HE [67]. By restoring a healthy gut microbiota composition, FMT can help to re-establish the balance between beneficial and pathogenic bacteria, thereby reducing the production of toxins in the gut and improving intestinal barrier function. Mechanistic investigations have found that FMT reduced the level of gut microbial toxins such as LPS and suppressed the TLR4/MyD88/NF-κB signaling pathway and its downstream pro-inflammatory products, both in the substantia nigra and the colon [68]. This, in turn, can lead to a reduction in systemic inflammation and neurotoxicity, ameliorating the symptoms of HE [13,20].

FMT introduces competitive microbial species that outcompete pathogens like *C. difficile*. A study showed that donor-derived *Bacteroides* and *Clostridium* species could colonize the recipient gut, displacing pathogenic strains. During the therapeutic process, there is an interplay between recipient- and donor-derived microbiota, in which the FMT outcome is significantly linked to the enterotype and taxonomic distance between the donor and recipient microbiota [69]. Currently, FMT is considered the most effective method for rebuilding the gut microbiota. With further improved understanding of the impact of gut microbiota imbalance on disease, FMT will become increasingly attractive for the treatment of HE [70,71].

Reduction of Gut-Microbe-Derived Toxins

One of the key mechanisms by which FMT exerts its therapeutic functions in HE is through the reduction of toxins produced by certain gut microbes; in particular, the reduction of ammonia. FMT can modify and modulate the gut microbiota to reduce the production of ammonia by enhancing the growth of bacteria that metabolize ammonia, such as *Lactobacillus* and *Bifidobacterium*, inhibiting the growth of ammonia-generating bacteria, such as *Proteobacteria,* and enhancing the conversion of ammonia to less toxic metabolites, such as urea and glutamine [72].

In addition to reducing ammonia production, FMT can decrease the levels of other gut-derived toxins, such as endotoxin and inflammatory cytokines. This can help to reduce systemic inflammation and neuroinflammation, which are important contributors to the pathogenesis of HE [73,74].

Improvement of Intestinal Barrier Function

Intestinal barrier dysfunction is a hallmark of liver cirrhosis and HE [75]. Increased intestinal permeability allows the translocation of gut-derived toxins and bacteria into the portal circulation, contributing to liver injury and systemic inflammation. FMT has been shown to improve the function of the intestinal barrier by promoting the growth of beneficial bacteria that produce SCFAs, which play important roles in maintaining the integrity of the intestinal epithelium [76,77]. The transplanted microbiota produce SCFAs such as butyrate, acetate, and propionate, which restore gut homeostasis and reduce inflammation [78]. Since the FMT-transplanted microbiota can also enhance expression of antimicrobial peptides in the gut, the procedure helps to re-establish colonization resistance to prevent pathogen overgrowth [79].

FMT can upregulate the level of tight junction proteins and downregulate pro-inflammatory cytokines, thereby preventing the leakage of bacterial products into the systemic circulation, reducing bacterial translocation and endotoxemia [80,81].

Modulation of Immune and Inflammatory Responses

HE is associated with chronic systemic inflammation driven by gut-derived endotoxins. FMT modulates the immune response by reducing circulating levels of pro-inflammatory cytokines (eg, IL-1α, IL-1β, TNF-α, and IL-6) and increasing the levels of anti-inflammatory mediators (eg, IL-10, IL-4, and IL-13) [73,82]. The gut microbiota play a crucial role in regulating immune and inflammatory responses. Dysbiosis in patients with HE is associated with an imbalance in the production of pro-inflammatory and anti-inflammatory cytokines, leading to systemic inflammation and neuroinflammation. FMT can modulate immune and inflammatory responses by restoring a healthy gut microbiota composition and promoting the growth of bacteria that produce anti-inflammatory metabolites, such as SCFAs [83].

FMT also modulates the host immune response by promoting the growth of anti-inflammatory bacteria such as *Faecalibacterium prausnitzii* and *Lactobacillus rhamnosus*, thereby reducing pro-inflammatory cytokines. After FMT, anti-inflammatory regulatory T cells (Tregs) were increased and levels of pro-inflammatory interleukins (IL-1α and IL-6) were decreased in patients with ulcerative colitis [84,85]. FMT can restore normal bile acid metabolism, which is often disrupted in dysbiosis. FMT was shown to normalize secondary bile acid production by inhibiting the germination of *C. difficile* spores [86], thereby alleviating hepatocyte and biliary injury [87].

Clinical Evidence Supporting FMT for HE

Therapeutic Implications

Modulation of gut microbiota has emerged as a promising therapeutic strategy for HE. Probiotics, prebiotics, and synbiotics have shown potential in restoring microbial balance and reducing ammonia levels [88,89]. Non-absorbable antibiotics like rifaximin are widely used to target gut bacteria and

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

reduce toxin production, and have been demonstrated to be effective in modulating gut microbiota composition and improving gut metabolites to prevent and treat systemic infection in patients with liver disease [90,91].

Although still in its early stages, with most of the results obtained from small studies and case reports (**Table 1**), FMT has also demonstrated efficacy in improving cognitive function and reducing hospitalizations in HE patients [92]. In an initial animal study, Shen et al found that by transplanting bacteria with low urease activity, the intestinal microbiome of mice was altered continuously, and the fecal ammonia level in mice with liver injury was reduced [93]. This discovery provided new ideas for the treatment of HE patients with FMT. Another study showed that FMT can effectively improve HE in terms of behavior and spatial learning ability of rats with acute liver failure, in a process that involves restoring intestinal mucosal permeability and reducing blood ammonia and pro-inflammatory cytokine levels [94].

One of the earliest clinical reports of FMT for HE was published in 2016. It described treatment of a patient with recurrent HE (patient experiencing recurrent episodes of HE) via colonoscopy [95]. After 4 FMTs, the patient showed a significant improvement in cognitive function and a reduction in ammonia level, suggesting that FMT may be a promising treatment option for patients with recurrent HE [95]. Since then, several studies have been published, reporting similar findings. For example, a randomized clinical trial by Bajaj et al assessed the safety and efficacy of FMT in patients with recurrent HE [19]. The study included 10 patients who received FMT via colonoscopy. They found that FMT was associated with a significant improvement in cognitive function, a reduction in ammonia level, and a decrease in the frequency of HE episodes. With results from this and other related studies, the authors concluded that FMT is a safe and effective treatment option for patients with recurrent HE [96,97].

In another randomized controlled trial (RCT) completed in 2017, 20 patients with recurrent HE, defined as at least 2 documented overt HE episodes and overall psychometric HE score (PHES) of about -8.0, were randomly assigned to the FMT group or the standard treatment (SOC) group. All patients received treatment with lactulose, rifaximin, and a proton pump inhibitor. The FMT group received a 5-day antibiotic pretreatment followed by a single FMT enema (from fecal donors rich in *Helicobacter pylori* and rumen bacteria). They were then followed up for 150 days. On the 20th day of follow-up, the cognitive abilities (PHES and EncephalApp Stroop test) of patients in the FMT group improved significantly in comparison with baseline, while there was no significant improvement in the SOC group. There was no significant difference in end-stage liver disease scores between the groups. In addition, the SOC group experienced 6 HE events, while the FMT group experienced none [19]. By increasing the follow-up time of these patients to 12-15 months, the authors assessed the long-term safety profile of the FMT group [24]. They found that, compared with the SOC group, in the FMT group, the number of hospitalizations and HE events were fewer (10 vs 1 and 8 vs 0, respectively). Moreover, the cognitive ability of patients in the FMT group also appeared to be better than that in the SOC group [98].

Another RCT evaluated the safety and efficacy of FMT in patients with minimal HE and rCDI [99]. During the 20 week follow-up, 4 patients experienced adverse events (readmission, HE recurrence, death), including 1 patient who died of HE recurrence within 2 months after surgery due to pneumonia complicated by sepsis. Their results showed that at week 20 after receiving FMT, the blood ammonia concentration of the remaining 9 patients significantly decreased from 96 to 74 μmol/L [100]. This study indicated that FMT can be safely administered and can continue to have a significant impact on eradication of rCDI and improvement of the quality of life of patients suffering from HE.

Long-Term Stability and Outcomes

Whether FMT can generate long-term and favorable stable changes in gut microbiota composition is crucial to clinical applicability of the procedure. In this regard, it was demonstrated that FMT recipients can maintain a stable donor-like microbiota profile for up to 12 months post-transplantation. After the initial FMT, 22.58% (7/31) of the recipients achieved clinical remission and endoscopy remission and the clinical response rate was 67.74% (21/31), which increased to 80% (16/20) after the second FMT. The 1- and 4-year relapse rates in the 12 remission patients were 33.33% and 58.3% [101]. Acharya et al demonstrated that FMT significantly improved cognitive performance and quality of life in HE patients over a 12-month follow-up period, with sustained benefits in microbiota diversity and ammonia levels [102]. Similarly, another RCT reported a 50% reduction in HE recurrence rates in FMT recipients compared with standard care over 18 months [98].

In 2 patients with HE treated with FMT after transjugular intrahepatic portosystemic shunt (TIPS) placement, HE was experienced more than twice within the month following the TIPS procedure and patients underwent 3 endoscopic FMT procedures. During the follow-up period of nearly a year, neither patient experienced HE again, and the liver function of patient 1 showed significant improvement. Except for transient constipation in patient 2, no other adverse events or infections related to FMT occurred [103]. In another FMT study involving 5 donors and 10 HE patients, the patients' cognitive function improved significantly after FMT, but the effect varied depending on donor and recipient factors [104]. Patients who responded

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

to FMT had higher levels of beneficial bacteria such as bifidobacteria at baseline and throughout the study period, while FMT donors with the poorest cognitive function had the lowest levels of fecal SCFA. In additional, FMT is also shown to be useful in treating pseudomembranous colitis, emphasizing the therapeutic potential of FMT in severe gastrointestinal conditions [105]. Taken together, these findings suggest that FMT may offer durable and long-term benefits by restoring gut microbial balance and improving cognitive function in HE patients.

However, long-term outcomes may vary depending on donor selection and patient characteristics. A study by Kao et al highlighted that FMT from a healthy donor with high microbial diversity was associated with better long-term outcomes, including reduced hospitalizations and improved liver function. They saw improvement in ammonia levels, inhibitory control test, and Stroop test after FMT in a patient with Grade I-II HE. Conversely, patients with advanced cirrhosis or comorbidities may experience attenuated benefits, underscoring the need for personalized approaches [20].

Safety of FMT

FMT is generally well-tolerated; most adverse events reported are mild and transient. Common adverse effects include abdominal discomfort, bloating, and diarrhea, which typically resolve within 48 hours, and serious adverse events, such as infections or adverse immune reactions, are rare [106]. A systematic review found no serious adverse events directly attributable to FMT in HE patients, supporting its safety profile [107]. Short-term safety of FMT has been demonstrated in the treatment of recurrent *C. difficile* infection, even in immunocompromised patients [24], with most reported adverse events being mild and self-limiting [108]. Data provided by Bajaj et al also supported the short-term (<1 year) safety of FMT [103]. Among the 20 patients included in these 2 studies, only 1 patient experienced sepsis-associated encephalopathy (SAE), but the data and safety monitoring committee considered it to be unrelated to the FMT.

Although there are currently some follow-up data, for about 1 year, more research and longer follow-up time data are still needed to explore the long-term safety issues of FMT. There are concerns that certain intestinal microbiota may cause chronic diseases, such as obesity, diabetes, colon cancer, and irritable bowel syndrome, in addition to the risk of infections and unhealthy long-term microbial alterations. A rare case of FMT transmission of drug-resistant Escherichia coli in an HE patient has been reported [109], supporting the concern that FMT can also carry certain risks. Studies have highlighted the transmission of multidrug-resistant organisms via FMT, emphasizing the need for rigorous donor screening [110,111]. Additionally, a study by Woodworth et al raised concerns about potential long-term changes in microbial composition, which could have unforeseen consequences [112]. These risks underscore the importance of standardized protocols and long-term monitoring. Therefore, it is necessary to strengthen donor screening to limit the spread of microorganisms that may cause adverse infection or colonization events.

The Advantage of FMT in Treating HE

FMT, as a method of reconstructing gut microbiota structure and adjusting metabolic processes and signaling pathways for patients with HE, has been shown to be able to significantly improve the cognitive function of HE patients and reduce readmission rate [19]. This suggests that this method can not only alleviate HE symptoms, but also effectively reduce the risk of illness, and the recurrence rate of the disease. In contrast, traditional treatment methods such as drug therapy and dietary therapies fall short of being able to fundamentally solve the problem of gut microbiota imbalance, although they can also alleviate HE to a certain extent. Furthermore, drug therapy may also cause adverse reactions and complications, while dietary therapy requires patients to adhere to it for a long time to be effective. Compared with rifaximin, a commonly used antibiotic for HE, FMT was more effective in reducing ammonia levels and improving cognitive outcomes [113]. Patients undergoing FMT reported better quality-of-life scores than patients on drug regimens. FMT not only improved cognitive function but also enhanced overall well-being, which is often not achieved with lactulose or rifaximin [114,115]. Furthermore, in comparison with drug-based intervention, FMT is well-tolerated, with a favorable safety profile. A meta-analysis concluded that FMT has fewer long-term adverse effects than prolonged use of rifaximin, the overuse of which can also lead to bacterial resistance [116]. Economically, although FMT is initially more expensive, it may be cost-effective in the long term due to reduced hospitalizations and recurrent HE episodes. An economic analysis by Tapper et al suggested that FMT could lower healthcare costs compared with lifelong rifaximin therapy [117].

Challenges and Future Directions

Standardization of FMT Procedures

One of the main challenges in FMT for the treatment of HE is the lack of standardization in FMT procedures. There is currently no consensus on the optimal route of administration, the timing and frequency of FMT, or the selection of donors. Most studies have used FMT via colonoscopy, but other routes of administration, such as oral capsules or nasoenteric tubes, have also been explored. The choice of route of administration

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

may influence the efficacy and safety of FMT, and further studies are needed to determine the optimal approach [7].

The selection of donors is a critical factor in the success of FMT. Donors should be carefully screened for infectious diseases, metabolic disorders, and other conditions that could affect the safety and efficacy of FMT. However, there is currently no standardized protocol for donor screening, and further research is needed to establish clinical guidelines for donor screening and selection [4].

Mechanisms of Action

The mechanisms underlying the therapeutic effects of FMT for HE are not fully understood, although several potential mechanisms have been proposed, including the restoration of gut microbiota composition, reduction of gut-derived toxins, improvement of intestinal barrier function, and modulation of immune and inflammatory responses. However, further research is needed to elucidate the specific mechanisms by which FMT exerts its therapeutic effects in HE patients [7]. In particular, research is needed to identify signaling molecules, including metabolites, neuromodulators, neuropeptides, and neurotransmitters in the gut microbiota that contribute to the therapeutic effects [118].

Long-Term Safety and Efficacy

The long-term safety and efficacy of FMT in HE patients are still not well assessed. Most studies have only evaluated short-term outcomes, and further research is needed to determine the long-term benefits and risks of FMT; in particular, the potential risks of FMT, such as infections, adverse immune reactions, and the transmission of antibiotic resistance genes [10].

Personalized FMT Approaches

Given the heterogeneity of gut microbiota composition and the multifactorial nature of HE, personalized approaches to FMT may be needed to optimize its efficacy. For example, donors should ideally be selected based on the recipient's gut microbiota profile, FMT could be targeted to address specific microbial imbalances, and the combination of FMT with other therapies, such as probiotics or prebiotics, may enhance the therapeutic effects of FMT in certain HE patients [7]. Cutting-edge technologies for microbiome assessment should be applied to profile both donor and recipient gut microbiota to ensure optimal therapeutic outcomes for individual patients, since the factors affecting FMT success are related to both donors and recipients (such as diversity and specific composition of the gut microbiome, immune system, genetics, and general health condition). Therapeutic outcomes are also dependent on clinical protocols, which should be optimized with respect to specific fecal quantity, timing and number of infusions, route of delivery, and associated adjuvant treatments [119]. Recent studies have explored the use of precision medicine approaches to tailor gut microbiota modulation based on individual microbial profiles. For instance, personalized probiotic formulations in FMT significantly improve cognitive outcomes in HE patients compared with standard therapies, and the role of gut virome modulation in reducing ammonia-producing bacteria may offer a novel avenue for treatment [120]. Additionally, advances in metabolomics have identified specific microbial metabolites, such as indoles and bile acids, as potential biomarkers and therapeutic targets for HE [7].

Integration with Other Therapies

FMT is not a standalone treatment for HE, and it should be integrated with other therapies, such as lactulose, rifaximin, and dietary modifications, to optimize patient outcomes. Issues that need to be addressed regarding current FMT treatment protocols for HE include whether antibiotic pretreatment is required before FMT, the optimal dosing regimen, and the selection and screening of donors. Several trials are underway to address these issues, with relatively large sample sizes, to determine the optimal combination of therapies and the timing of FMT in the treatment of HE [121].

Limitations

There are several limitations and challenges associated with FMT for HE. Firstly, the optimal treatment duration for patients with different HE remains largely undefined. Large-scale RCTs are necessary to develop and validate standardized clinical FMT protocols [70]. Additionally, FMT parameters and outcome measures such as donor selection, optimal dosage, timing, administration route, and use of antibiotics need further investigation and optimization, and long-term effects need more study [122]. More studies are also needed to address possible adverse events observed in previous studies [15,70].

Conclusions

FMT has been demonstrated to be a promising therapeutic strategy for the treatment of HE. It has the potential to improve gut microbiota composition, reduce gut-derived toxins, improve intestinal barrier function, and modulate immune and inflammatory responses. The available evidence suggests that FMT is safe and effective in improving cognitive function, reducing ammonia levels, and decreasing the frequency of HE episodes. However, further research is needed to standardize FMT procedures, elucidate the mechanisms of action, evaluate the long-term safety and efficacy, and develop personalized approaches to FMT for HE. With continued research and

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

clinical trials, FMT may become an important and supplementary tool in the management of HE, offering hope for improved outcomes and quality of life for patients with this debilitating condition. FMT has become a gold-standard treatment for rCDI, with cure rates of 80-90%, far surpassing conventional antibiotics like vancomycin. Its success lies in restoring microbial diversity and displacing pathogenic *C. difficile* through competitive exclusion and metabolic modulation (eg, SCFA production). Optimal outcomes depend on rigorous donor screening (eg, BMI <30, young age, high microbial diversity) and emerging predictive algorithms (eg, iMic) that use donor microbiome data to forecast engraftment success and clinical response without recipient profiling. While challenges like recipient variability persist, advances in donor-recipient matching, administration methods, and synthetic microbiota are paving the way for broader clinical adoption.

Availability of Data and Materials

Available upon request.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Wright G, Jalan R. Management of hepatic encephalopathy in patients with cirrhosis. Best Pract Res Clin Gastroenterol. 2007;21(1):95-110
2. Lu K. Cellular pathogenesis of hepatic encephalopathy: An update. Biomolecules. 2023;13(2):396
3. Rocco A, Sgamato C, Compare D, et al. Gut microbes and hepatic encephalopathy: From the old concepts to new perspectives. Front Cell Dev Biol. 2021;9:748253
4. Montagnese S, Russo FP, Amodio P, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis. 2019;51(2):190-205
5. Rudler M, Weiss N, Bouzbib C, Thabut D. Diagnosis and management of hepatic encephalopathy. Clin Liver Dis. 2021;25(2):393-417
6. Alsahhar JS, Rahimi RS. Updates on the pathophysiology and therapeutic targets for hepatic encephalopathy. Curr Opin Gastroenterol. 2019;35(3):145-54
7. Lu H, Zhang H, Wu Z, Li L. Microbiota-gut-liver-brain axis and hepatic encephalopathy. Microbiome Res Rep. 2024;3(2):17
8. Ahluwalia V, Betrapally NS, Hylemon PB, et al. Impaired gut-liver-brain axis in patients with cirrhosis. Sci Rep. 2016;6:26800
9. Bajaj JS, Hylemon PB, Ridlon JM, et al. Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. Am J Physiol Gastrointest Liver Physiol. 2012;303(6):G675-85
10. Shawcross D, Jalan R. The pathophysiologic basis of hepatic encephalopathy: Central role for ammonia and inflammation. Cell Mol Life Sci. 2005;62(19-20):2295-304
11. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715-35
12. Rose CF, Amodio P, Bajaj JS, et al. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatol. 2020;73(6):1526-47
13. Bajaj JS, Khoruts A. Microbiota changes and intestinal microbiota transplantation in liver diseases and cirrhosis. J Hepatol. 2020;72(5):1003-27
14. Maslennikov R, Alieva A, Poluektova E, et al. Sarcopenia in cirrhosis: Prospects for therapy targeted to gut microbiota. World J Gastroenterol. 2023;29(27):4236-51
15. Wang JW, Kuo CH, Kuo FC, et al. Fecal microbiota transplantation: Review and update. J Formos Med Assoc. 2019;118(Suppl. 1):S23-S31
16. Ooijevaar RE, Terveer EM, Verspaget HW, et al. Clinical application and potential of fecal microbiota transplantation. Annu Rev Med. 2019;70:335-51
17. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017;66(4):569-80
18. Mullish BH, McDonald JAK, Thursz MR, Marchesi JR. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. Hepatology. 2017;66(4):1354-55
19. Bajaj JS, Kassam Z, Fagan A, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. Hepatology. 2017;66(6):1727-38
20. Kao D, Roach B, Park H, et al. Fecal microbiota transplantation in the management of hepatic encephalopathy. Hepatology. 2016;63(1):339-40
21. Kang DW, Adams JB, Gregory AC, et al. Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: An open-label study. Microbiome. 2017;5(1):10
22. Yadegar A, Bar-Yoseph H, Monaghan TM, et al. Fecal microbiota transplantation: current challenges and future landscapes. Clin Microbiol Rev. 2024;37(2):e0006022
23. Smits LP, Bouter KE, de Vos WM, et al. Therapeutic potential of fecal microbiota transplantation. Gastroenterology. 2013;145(5):946-53
24. Kelly CR, Kahn S, Kashyap P, et al. Update on fecal microbiota transplantation 2015: Indications, methodologies, mechanisms, and outlook. Gastroenterology. 2015;149(1):223-37
25. Taha AM, Abouelmagd K, Nada SA, et al. Impact of fecal microbiota transplantation in severe alcoholic hepatitis: A systematic review and meta-analysis. JGH Open. 2024;8(8):e70007
26. Medini D, Serruto D, Parkhill J, et al. Microbiology in the post-genomic era. Nat Rev Microbiol. 2008;6(6):419-30
27. Deng P, Swanson KS. Gut microbiota of humans, dogs and cats: Current knowledge and future opportunities and challenges. Br J Nutr. 2015;113(Suppl.):S6-17
28. Mathur R, Barlow GM. Obesity and the microbiome. Expert Rev Gastroenterol Hepatol. 2015;9(8):1087-99
29. Feng Q, Chen WD, Wang YD. Gut microbiota: An integral moderator in health and disease. Front Microbiol. 2018;9:151
30. Liu J, Xu Y, Jiang B. Novel insights into pathogenesis and therapeutic strategies of hepatic encephalopathy, from the gut microbiota perspective. Front Cell Infect Microbiol. 2021;11:586427
31. Hao Y, Hao Z, Zeng X, Lin Y. Gut microbiota and metabolites of cirrhotic portal hypertension: A novel target on the therapeutic regulation. J Gastroenterol. 2024;59(9):788-97
32. Fang J, Yu CH, Li XJ, et al. Gut dysbiosis in nonalcoholic fatty liver disease: Pathogenesis, diagnosis, and therapeutic implications. Front Cell Infect Microbiol. 2022;12:997018
33. Shen J, Obin MS, Zhao L. The gut microbiota, obesity and insulin resistance. Mol Aspects Med. 2013;34(1):39-58
34. Dalal S, Ramirez-Gomez J, Sharma B, et al. MicroRNAs and synapse turnover in Alzheimer's disease. Ageing Res Rev. 2024;99:102377
35. Chen X, Xu L, Chen Q, et al. Polystyrene micro- and nanoparticles exposure induced anxiety-like behaviors, gut microbiota dysbiosis and metabolism disorder in adult mice. Ecotoxicol Environ Saf. 2023;259:115000
36. Ahluwalia B, Moraes L, Magnusson MK, Ohman L. Immunopathogenesis of inflammatory bowel disease and mechanisms of biological therapies. Scand J Gastroenterol. 2018;53(4):379-89
37. Zhang T, Gao G, Kwok LY, Sun Z. Gut microbiome-targeted therapies for Alzheimer's disease. Gut Microbes. 2023;15(2):2271613
38. Thurman RG, Bradford BU, Iimuro Y, et al. The role of gut-derived bacterial toxins and free radicals in alcohol-induced liver injury. J Gastroenterol Hepatol. 1998;13(Suppl.):S39-50

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

39. Birg A, van der Horn HJ, Ryman SG, et al. Diffusion magnetic resonance spectroscopy captures microglial reactivity related to gut-derived systemic lipopolysaccharide: A preliminary study. Brain Behav Immun. 2024;122:345-52
40. Zhang Z, Zhai H, Geng J, et al. Large-scale survey of gut microbiota associated with MHE Via 16S rRNA-based pyrosequencing. Am J Gastroenterol. 2013;108(10):1601-11
41. Claeys W, Van Hoecke L, Lefere S, et al. The neurogliovascular unit in hepatic encephalopathy. JHEP Rep. 2021;3(5):100352
42. Parekh PJ, Balart LA. Ammonia and its role in the pathogenesis of hepatic encephalopathy. Clin Liver Dis. 2015;19(3):529-37
43. Norenberg MD, Rao KV, Jayakumar AR. Mechanisms of ammonia-induced astrocyte swelling. Metab Brain Dis. 2005;20(4):303-18
44. Liu P, Li H, Xu H, et al. Chitooligosaccharides attenuated hepatic encephalopathy in mice through stabilizing gut-liver-brain disturbance. Mol Nutr Food Res. 2023;67(1):e2200158
45. Brown GC. The endotoxin hypothesis of neurodegeneration. J Neuroinflammation. 2019;16(1):180
46. Bloom PP, Luevano JM Jr., Miller KJ, Chung RT. Deep stool microbiome analysis in cirrhosis reveals an association between short-chain fatty acids and hepatic encephalopathy. Ann Hepatol. 2021;25:100333
47. Baraldi M, Pinelli G, Ricci P, Zeneroli ML. Toxins in hepatic encephalopathy: The role of the synergistic effect of ammonia, mercaptans and short chain fatty acids. Arch Toxicol Suppl. 1984;7:103-5
48. Wang P, Mi Y, Yu H, et al. Trimethylamine-N-oxide aggravated the sympathetic excitation in D-galactose induced aging rats by down-regulating P2Y12 receptor in microglia. Biomed Pharmacother. 2024;174:116549
49. Jaffe A, Lim JK, Jakab SS. Pathophysiology of hepatic encephalopathy. Clin Liver Dis. 2020;24(2):175-88
50. Kroupina K, Bemeur C, Rose CF. Amino acids, ammonia, and hepatic encephalopathy. Anal Biochem. 2022;649:114696
51. Bajaj JS, Ridlon JM, Hylemon PB, et al. Linkage of gut microbiome with cognition in hepatic encephalopathy. Am J Physiol Gastrointest Liver Physiol. 2012;302(1):G168-75
52. Sung CM, Lin YF, Chen KF, et al. Predicting clinical outcomes of cirrhosis patients with hepatic encephalopathy from the fecal microbiome. Cell Mol Gastroenterol Hepatol. 2019;8(2):301-18.e2
53. Kang EJ, Cha MG, Kwon GH, et al. Akkermansia muciniphila improve cognitive dysfunction by regulating BDNF and serotonin pathway in gut-liver-brain axis. Microbiome. 2024;12(1):181
54. Ansari A, Bose S, Lim SK, et al. Combination of *Scutellaria baicalensis* and metformin ameliorates diet-induced metabolic dysregulation in mice via the gut-liver-brain axis. Am J Chin Med. 2020;48(6):1409-33
55. Chen Z, Ruan J, Li D, et al. The role of intestinal bacteria and gut-brain axis in hepatic encephalopathy. Front Cell Infect Microbiol. 2020;10:595759
56. He X, Hu M, Xu Y, et al. The gut-brain axis underlying hepatic encephalopathy in liver cirrhosis. Nat Med. 2025;31(2):627-38
57. Wiest R, Albillos A, Trauner M, et al. Targeting the gut-liver axis in liver disease. J Hepatol. 2017;67(5):1084-103
58. Ding JH, Jin Z, Yang XX, et al. Role of gut microbiota via the gut-liver-brain axis in digestive diseases. World J Gastroenterol. 2020;26(40):6141-62
59. Giuli L, Maestri M, Santopaolo F, et al. Gut microbiota and neuroinflammation in acute liver failure and chronic liver disease. Metabolites. 2023;13(6):772
60. Bajaj JS, Kamath PS, Reddy KR. The evolving challenge of infections in cirrhosis. N Engl J Med. 2021;384(24):2317-30
61. Acharya C, Bajaj JS. Gut microbiota and complications of liver disease. Gastroenterol Clin North Am. 2017;46(1):155-69
62. Doenyas C, Clarke G, Cserjesi R. Gut-brain axis and neuropsychiatric health: Recent advances. Sci Rep. 2025;15(1):3415
63. Margolis KG, Cryan JF, Mayer EA. The microbiota-gut-brain axis: From motility to mood. Gastroenterology. 2021;160(5):1486-501
64. Yang C, Hu T, Xue X, et al. Multi-omics analysis of fecal microbiota transplantation's impact on functional constipation and comorbid depression and anxiety. BMC Microbiol. 2023;23(1):389
65. Won SM, Oh KK, Gupta H, et al. The link between gut microbiota and hepatic encephalopathy. Int J Mol Sci. 2022;23(16):8999
66. Li M, Li K, Tang S, et al. Restoration of the gut microbiota is associated with a decreased risk of hepatic encephalopathy after TIPS. JHEP Rep. 2022;4(5):100448
67. Wilson BC, Vatanen T, Cutfield WS, O'Sullivan JM. The super-donor phenomenon in fecal microbiota transplantation. Front Cell Infect Microbiol. 2019;9:2
68. Zhao Z, Ning J, Bao XQ, et al. Fecal microbiota transplantation protects rotenone-induced Parkinson's disease mice via suppressing inflammation mediated by the lipopolysaccharide-TLR4 signaling pathway through the microbiota-gut-brain axis. Microbiome. 2021;9(1):226
69. He R, Li P, Wang J, et al. The interplay of gut microbiota between donors and recipients determines the efficacy of fecal microbiota transplantation. Gut Microbes. 2022;14(1):2100197
70. Tun KM, Hong AS, Batra K, Naga Y, Ohning G. A systematic review of the efficacy and safety of fecal microbiota transplantation in the treatment of hepatic encephalopathy and *Clostridioides difficile* infection in patients with cirrhosis. Cureus. 2022;14(5):e25537
71. Ma Z, Akhtar M, Pan H, et al. Fecal microbiota transplantation improves chicken growth performance by balancing jejunal Th17/Treg cells. Microbiome. 2023;11(1):137
72. Shah YR, Ali H, Tiwari A, et al. Role of fecal microbiota transplant in management of hepatic encephalopathy: Current trends and future directions. World J Hepatol. 2024;16(1):17-32
73. Zhang WH, Jin ZY, Yang ZH, et al. Fecal microbiota transplantation ameliorates active ulcerative colitis by downregulating pro-inflammatory cytokines in mucosa and serum. Front Microbiol. 2022;13:818111
74. Weingarden AR, Vaughn BP. Intestinal microbiota, fecal microbiota transplantation, and inflammatory bowel disease. Gut Microbes. 2017;8(3):238-52
75. Gerova VA, Svinarov DA, Nakov RV, et al. Intestinal barrier dysfunction in liver cirrhosis assessed by iohexol test. Eur Rev Med Pharmacol Sci. 2020;24(1):315-22
76. Chen R, Xu Y, Wu P, et al. Transplantation of fecal microbiota rich in short chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota. Pharmacol Res. 2019;148:104403
77. Cui M, Xiao H, Li Y, et al. Faecal microbiota transplantation protects against radiation-induced toxicity. EMBO Mol Med. 2017;9(4):448-61
78. Pant K, Venugopal SK, Lorenzo Pisarello MJ, Gradilone SA. The role of gut microbiome-derived short-chain fatty acid butyrate in hepatobiliary diseases. Am J Pathol. 2023;193(10):1455-67
79. Ducarmon QR, Zwittink RD, Hornung BVH, et al. Gut microbiota and colonization resistance against bacterial enteric infection. Microbiol Mol Biol Rev. 2019;83(3):e00007-19
80. Zhou Z, Bian C, Luo Z, et al. Progesterone decreases gut permeability through upregulating occludin expression in primary human gut tissues and Caco-2 cells. Sci Rep. 2019;9(1):8367
81. Cheng S, Ma X, Geng S, et al. Fecal microbiota transplantation beneficially regulates intestinal mucosal autophagy and alleviates gut barrier injury. mSystems. 2018;3(5):e00137-18
82. Zhang W, Zou G, Li B, et al. Fecal microbiota transplantation (FMT) alleviates experimental colitis in mice by gut microbiota regulation. J Microbiol Biotechnol. 2020;30(8):1132-41
83. Martin-Gallausiaux C, Marinelli L, Blottiere HM, et al. SCFA: Mechanisms and functional importance in the gut. Proc Nutr Soc. 2021;80(1):37-49
84. Lee SD. Health maintenance in ulcerative colitis. Gastroenterol Clin North Am. 2020;49(4):xv-xvi
85. Wang Y, Wiesnoski DH, Helmink BA, et al. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. Nat Med. 2018;24(12):1804-8
86. Weingarden AR, Chen C, Bobr A, et al. Microbiota transplantation restores normal fecal bile acid composition in recurrent *Clostridium difficile* infection. Am J Physiol Gastrointest Liver Physiol. 2014;306(4):G310-19
87. Li M, Cai SY, Boyer JL. Mechanisms of bile acid mediated inflammation in the liver. Mol Aspects Med. 2017;56:45-53
88. Weir V, Reddy KR. Nonpharmacologic management of hepatic encephalopathy: An update. Clin Liver Dis. 2020;24(2):243-61
89. Shukla S, Shukla A, Mehboob S, Guha S. Meta-analysis: The effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy. Aliment Pharmacol Ther. 2011;33(6):662-71
90. Kang DJ, Kakiyama G, Betrapally NS, et al. Rifaximin exerts beneficial effects independent of its ability to alter microbiota composition. Clin Transl Gastroenterol. 2016;7(8):e187

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

91. Odenwald MA, Lin H, Lehmann C, et al. Bifidobacteria metabolize lactulose to optimize gut metabolites and prevent systemic infection in patients with liver disease. Nat Microbiol. 2023;8(11):2033-49
92. Ilie OD, Duta R, Nita IB, et al. A comprehensive overview of the past, current, and future randomized controlled trials in hepatic encephalopathy. Medicina (Kaunas). 2023;59(12):2143
93. Shen TC, Albenberg L, Bittinger K, et al. Engineering the gut microbiota to treat hyperammonemia. J Clin Invest. 2015;125(7):2841-50
94. Wang WW, Zhang Y, Huang XB, et al. Fecal microbiota transplantation prevents hepatic encephalopathy in rats with carbon tetrachloride-induced acute hepatic dysfunction. World J Gastroenterol. 2017;23(38):6983-94
95. Kao D, Roach B, Silva M, et al. Effect of oral capsule- vs colonoscopy-delivered fecal microbiota transplantation on recurrent *Clostridium difficile* infection: A randomized clinical trial. JAMA. 2017;318(20):1985-93
96. Fischer M, Kao D, Kelly C, et al. Fecal microbiota transplantation is safe and efficacious for recurrent or refractory *Clostridium difficile* infection in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2016;22(10):2402-9
97. Cheng YW, Alhaffar D, Saha S, et al. Fecal microbiota transplantation is safe and effective in patients with *Clostridioides difficile* infection and cirrhosis. Clin Gastroenterol Hepatol. 2021;19(8):1627-34
98. Bajaj JS, Fagan A, Gavis EA, et al. Long-term outcomes of fecal microbiota transplantation in patients with cirrhosis. Gastroenterology. 2019;156(6):1921-23.e3
99. Mehta SR, Yen EF. Microbiota-based therapies *Clostridioides difficile* infection that is refractory to antibiotic therapy. Transl Res. 2021;230:197-207
100. Mehta R, Kabrawala M, Nandwani S, et al. Preliminary experience with single fecal microbiota transplant for treatment of recurrent overt hepatic encephalopathy – a case series. Indian J Gastroenterol. 2018;37(6):559-62
101. Ren R, Gao X, Shi Y, et al. Long-term efficacy of low-intensity single donor fecal microbiota transplantation in ulcerative colitis and outcome-specific gut bacteria. Front Microbiol. 2021;12:742255
102. Acharya C, Bajaj JS. Current management of hepatic encephalopathy. Am J Gastroenterol. 2018;113(11):1600-12
103. Bajaj JS, Salzman NH, Acharya C, et al. Fecal microbial transplant capsules are safe in hepatic encephalopathy: A phase 1, randomized, placebo-controlled trial. Hepatology. 2019;70(5):1690-703
104. Bloom PP, Donlan J, Torres Soto M, et al. Fecal microbiota transplant improves cognition in hepatic encephalopathy and its effect varies by donor and recipient. Hepatol Commun. 2022;6(8):2079-89
105. Huang GQ, Bai Y, Sun ZQ, Liu J. Successful treatment of pseudomembranous colitis with fecal microbiota transplantation – a case study on a patient rescued by extracorporeal cardiopulmonary resuscitation after cardiac arrest. Ann Transplant. 2020;25:e923283
106. Cammarota G, Ianiro G, Kelly CR, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut. 2019;68(12):2111-21
107. Bajaj JS, Hays RA. Manipulation of the gut-liver axis using microbiome restoration therapy in primary sclerosing cholangitis. Am J Gastroenterol. 2019;114(7):1027-29
108. Afecto E, Ponte A, Fernandes S, et al. Fecal microbiota transplantation in hepatic encephalopathy: A review of the current evidence and future perspectives. Acta Gastroenterol Belg. 2021;84(1):87-90
109. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. N Engl J Med. 2019;381(21):2043-50
110. Gupta S, Mullish BH, Allegretti JR. Fecal microbiota transplantation: The evolving risk landscape. Am J Gastroenterol. 2021;116(4):647-56
111. Mehta N, Wang T, Friedman-Moraco RJ, et al. Fecal microbiota transplantation donor screening updates and research gaps for solid organ transplant recipients. J Clin Microbiol. 2022;60(2):e0016121
112. Woodworth MH, Conrad RE, Haldopoulos M, et al. Fecal microbiota transplantation promotes reduction of antimicrobial resistance by strain replacement. Sci Transl Med. 2023;15(720):eabo2750
113. Bloom PP, Tapper EB, Young VB, Lok AS. Microbiome therapeutics for hepatic encephalopathy. J Hepatol. 2021;75(6):1452-64
114. Rajpurohit S, Musunuri B, Shailesh, et al. Novel drugs for the management of hepatic encephalopathy: Still a long journey to travel. J Clin Exp Hepatol. 2022;12(4):1200-14
115. Mahpour NY, Pioppo-Phelan L, Reja M, et al. Pharmacologic management of hepatic encephalopathy. Clin Liver Dis. 2020;24(2):231-42
116. Xu D, Chen VL, Steiner CA, et al. Efficacy of fecal microbiota transplantation in irritable bowel syndrome: A systematic review and meta-analysis. Am J Gastroenterol. 2019;114(7):1043-50
117. Varier RU, Biltaji E, Smith KJ, et al. Cost-effectiveness analysis of fecal microbiota transplantation for recurrent *Clostridium difficile* infection. Infect Control Hosp Epidemiol. 2015;36(4):438-44
118. Liu L, Wu Q, Chen Y, et al. Gut microbiota in chronic pain: Novel insights into mechanisms and promising therapeutic strategies. Int Immunopharmacol. 2023;115:109685
119. Porcari S, Benech N, Valles-Colomer M, et al. Key determinants of success in fecal microbiota transplantation: From microbiome to clinic. Cell Host Microbe. 2023;31(5):712-33
120. Rackayova V, Flatt E, Braissant O, et al. Probiotics improve the neurometabolic profile of rats with chronic cholestatic liver disease. Sci Rep. 2021;11(1):2269
121. Stoy S, Eriksen LL, Lauszus JS, et al. Cirrhosis and faecal microbiota transplantation (ChiFT) protocol: A Danish multicentre, randomised, placebo-controlled trial in patients with decompensated liver cirrhosis. BMJ Open. 2025;15(2):e091078
122. Singh P, Alm EJ, Kelley JM, et al. Effect of antibiotic pretreatment on bacterial engraftment after fecal microbiota transplant (FMT) in IBS-D. Gut Microbes. 2022;14(1):2020067
123. Philips CA, Pande A, Shasthry SM, et al. Healthy donor fecal microbiota transplantation in steroid-ineligible severe alcoholic hepatitis: A pilot study. Clin Gastroenterol Hepatol. 2017;15(4):600-2
124. Bajaj JS, Gavis EA, Fagan A, et al. A randomized clinical trial of fecal microbiota transplant for alcohol use disorder. Hepatology. 2021;73(5):1688-700
125. Philips CA, Ahamed R, Rajesh S, et al. Clinical outcomes and gut microbiota analysis of severe alcohol-associated hepatitis patients undergoing healthy donor fecal transplant or pentoxifylline therapy: Single-center experience from Kerala. Gastroenterol Rep (Oxf). 2022;10:goac074
126. Bajaj JS, Fagan A, Gavis EA, et al. Microbiota transplant for hepatic encephalopathy in cirrhosis: The THEMATIC trial. J Hepatol. 2025;83(1):81-91

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]