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MINIREVIEWS

Fecal microbiota transplantation: A promising treatment strategy for chronic liver disease

Lei Ma, Meng-Han Zhang, Yi-Fan Xu, Yan-Xu Hao, Xuan-Xuan Niu, Yan Li, Hui-Chun Xing

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Lei Ma, Meng-Han Zhang, Yi-Fan Xu, Yan-Xu Hao, Xuan-Xuan Niu, Yan Li, Hui-Chun Xing, Center of Liver Diseases Division 3, Beijing Ditan Hospital, Capital Medical University, Beijing 100015, China

Hui-Chun Xing, Center of Liver Diseases Division 3, Peking University Ditan Teaching Hospital, Beijing 100015, China

Corresponding author: Hui-Chun Xing, MD, PhD, Chief Physician, Professor, Center of Liver Diseases Division 3, Beijing Ditan Hospital, Capital Medical University, No. 8 Jingshun East Street, Chaoyang District, Beijing 100015, China. hchxing@sohu.com

Abstract

Chronic liver disease has become a global health crisis, with increasing incidence and mortality rates placing a substantial burden on healthcare systems worldwide. A key factor in the progression of chronic liver disease is intestinal microbiota dysbiosis, which influences liver function *via* the intricate liver-gut axis. This axis plays a central role in various physiological processes, and disruptions in microbial composition can exacerbate liver pathology. Fecal microbiota transplantation (FMT) has emerged as a promising therapeutic strategy, with the potential to restore the composition and metabolic functions of the intestinal microbiota. Supported by encouraging findings from clinical trials and animal studies, FMT has demonstrated therapeutic benefits, including improvements in clinical symptoms, objective indicators, and long-term prognosis. These benefits encompass reductions in hepatic lipid deposition and inflammation, mitigation of complications in advanced liver disease, promotion of hepatitis B e antigen seroconversion, and enhancement of cognitive function. Although clinical evidence remains preliminary, current data underscore the transformative potential of FMT in managing chronic liver diseases. Nonetheless, challenges persist, including the need for standardized procedures, variability among donors, potential risks, and concerns regarding long-term safety. This review provides a comprehensive evaluation of the current literature on the efficacy and safety of FMT, while exploring future research directions to expand its application in liver disease management.

Key Words: Chronic liver disease; Fecal microbiota transplantation; Intestinal microbiota; Liver-gut axis; Clinical efficacy

Core Tip: Fecal microbiota transplantation shows significant potential in treating chronic liver diseases by improving liver inflammation, biomarkers, lipid metabolism, and cognitive function. It works through the liver-gut axis, restoring intestinal microbiota balance. Despite promising results, challenges remain in donor selection, standard treatment protocols, and long-term safety. Ongoing clinical trials and further research are needed to refine protocols and establish standardized approaches for optimal efficacy and safety in managing chronic liver diseases.

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INTRODUCTION

Chronic liver disease, one of the most prevalent global conditions, has become a significant burden due to rising incidence and mortality rates. It encompasses disorders such as metabolic dysfunction-associated steatotic liver disease [MASLD, formerly known as non-alcoholic fatty liver disease (NAFLD)], alcoholic liver disease (ALD), chronic viral hepatitis, drug-related liver disease, and autoimmune liver disease, all of which can progress to cirrhosis and liver cancer. In accordance with current nomenclature guidelines, this manuscript adopts the term MASLD. However, in sections discussing studies on fecal microbiota transplantation (FMT), original terms such as NAFLD are retained to accurately reflect the terminology used by the original authors, thereby maintaining fidelity to the cited sources. The progression of chronic liver disease is influenced by a complex interplay of factors. Recent studies have underscored the critical role of the intestinal microbiota in both the onset and progression of chronic liver disease[1,2]. This dynamic ecosystem is shaped by factors such as delivery method, race, age, sex, diet, comorbidities, and medications[3], and plays a central role in nutrient absorption and immune regulation. Dysbiosis-characterized by alterations in the composition, diversity, stability, and function of the microbiota-reflects a shift from a healthy to a disease-associated profile. Such imbalances can contribute to disease progression *via* the liver-gut axis and are correlated with disease severity.

FMT is an innovative and increasingly studied therapeutic approach aimed at restoring microbial balance by transferring processed fecal material from a healthy donor into the gastrointestinal tract of a recipient. The procedure typically involves several key steps: Screening donors to ensure safety and rule out transmissible diseases; processing fecal samples into a transplantable form; administering the material *via* the upper or lower gastrointestinal tract (commonly through colonoscopy, nasogastric/nasojejunal tube, enema, or oral capsules); and conducting clinical follow-up to assess treatment efficacy, safety, and potential adverse events. FMT has shown the potential to re-establish microbial homeostasis, enhance intestinal barrier integrity, reduce inflammation, and influence liver-related outcomes, demonstrating promise in improving the prognosis of various diseases (Figure 1).

This review provides a comprehensive overview of the development and application of FMT in chronic liver disease, highlighting its transformative potential in current and future treatment strategies. By examining its role in liver disease management, this review emphasizes FMT's emerging significance as a groundbreaking therapeutic approach, offering critical insights into how it could reshape the treatment landscape and pave the way for future innovations in this rapidly evolving field.

FMT AND LIVER DISEASE

The therapeutic mechanism of FMT in chronic liver disease was based on the liver-gut axis, an intricate network involving the intestinal microbiota, liver, portal vein, and biliary tract (Figure 2). The intestinal barrier served as the first line of defense in maintaining the homeostasis of this axis and comprised the intestinal epithelial barrier, mucus barrier, and immune barrier. Intestinal epithelial cells, goblet cells, Paneth cells, and enteroendocrine cells formed the epithelial barrier through tight junction proteins that tightly connected adjacent cells. Goblet cells secreted a thick mucus layer rich in highly glycosylated mucins, mainly mucin 2, forming the mucus barrier. Immune cells within the intestine contributed to the immune barrier. Paneth cells produced various antimicrobial peptides (AMPs), such as defensins and lysozyme, which exhibited innate antimicrobial activity and helped prevent the overgrowth of pathogenic bacteria. Due to their structural diversity and membrane-targeting mechanisms, most bacteria were unlikely to develop resistance to AMPs. Collectively, these barriers separated the intestinal microbiota from host immune cells, preventing excessive inflammatory responses and allowing microbiota to interact with the host indirectly through metabolites. Short-chain fatty acids (SCFAs) and secondary bile acids (BAs) were two major metabolites produced by the microbiota. SCFAs and BAs maintained intestinal barrier integrity and modulated immune responses through multiple pathways, enhancing anti-inflammatory effects and mitigating liver damage[4,5]. Under physiological conditions, microbe-associated molecular patterns (MAMPs)-originating from gut microbiota, such as lipopolysaccharide (LPS), peptidoglycan, and bacterial DNA-remained concealed within the gut to prevent unnecessary immune activation.

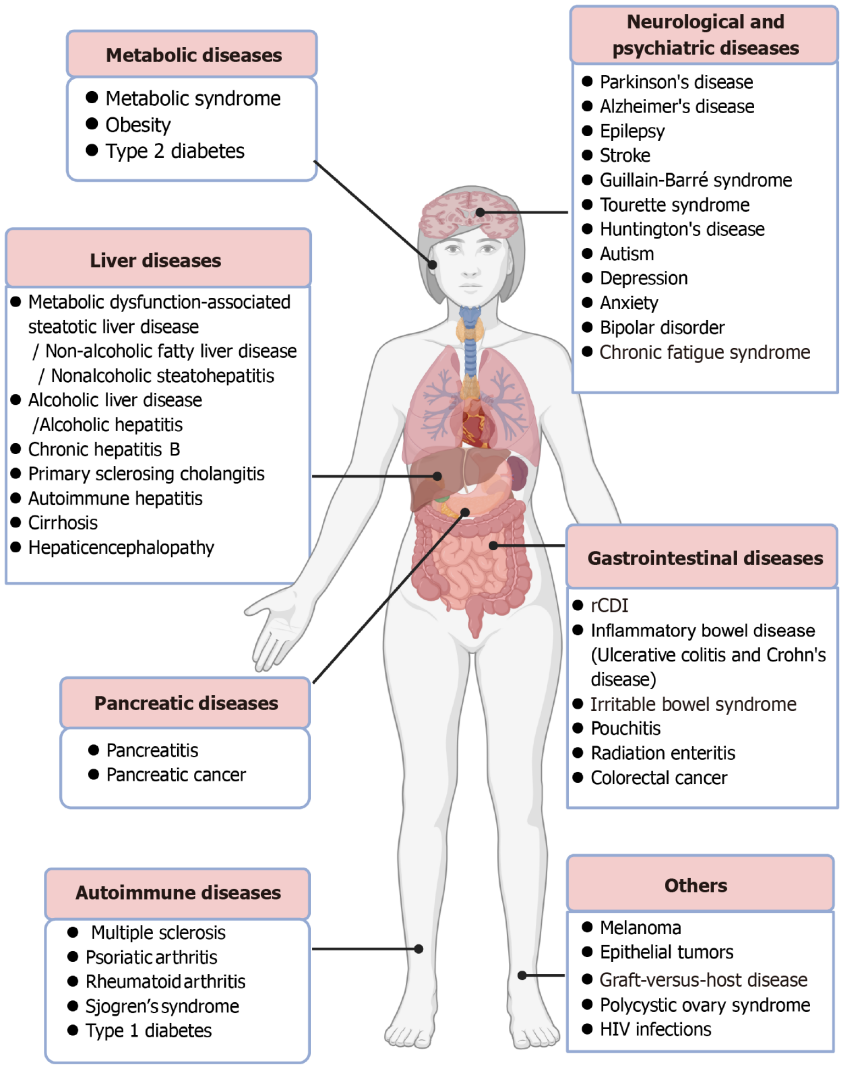

Figure 1 Applications of fecal microbiota transplantation in infectious and noninfectious diseases. Besides recurrent *Clostridium difficile* infection, the applications of fecal microbiota transplantation have been extended to noninfectious diseases, including neuropsychiatric diseases, metabolic diseases, digestive diseases, autoimmune diseases, and other diseases such as melanoma, epithelial tumors, graft-versus-host disease, and polycystic ovary syndrome. HIV: Human immunodeficiency virus; rCDI: Recurrent *Clostridium difficile* infection. Created with BioRender (Supplementary material).

However, in chronic liver disease, this homeostasis was disrupted. A key feature was small intestinal bacterial overgrowth (SIBO), particularly common in patients with portal hypertension and spontaneous bacterial peritonitis[6]. SIBO involved either an abnormally high bacterial load in the small intestine or a shift in microbiota composition, typically marked by overgrowth of colonic bacteria. Several factors contributed to SIBO in liver disease. In cirrhosis, portal hypertension led to intestinal congestion and reduced gut motility, promoting bacterial stasis[7]. Long-term use of proton pump inhibitors in these patients reduced gastric acid secretion, weakening the stomach's natural defense and increasing susceptibility to bacterial colonization[8]. Both SIBO and gut dysbiosis elevated levels of LPS, which downregulated tight junction proteins and impaired the intestinal barrier. When hepatocyte damage and barrier permeability increased, bacteria and MAMPs translocated *via* the portal vein to the liver, activating Toll-like receptors (TLRs) on Kupffer cells and hepatic stellate cells. Activated TLRs triggered downstream signaling cascades, promoted a pro-inflammatory state in the liver, and upregulated downstream pro-inflammatory cytokines. This inflammatory cascade contributed to the progression of liver fibrosis[9].

Patients with chronic liver disease exhibited a significantly altered intestinal microbiota composition compared to healthy controls[10,11]. Moreover, the severity of intestinal microbiota dysbiosis was closely associated with the extent of intestinal barrier damage and the progression of liver disease, including hepatic inflammation, fibrosis, cirrhosis, and carcinogenesis, regardless of etiology[12]. For example, *Klebsiella pneumoniae* (*K. pneumoniae*) was found to be closely associated with the development of fatty liver disease. This bacterium produced ethanol, which induced mitochondrial dysfunction in hepatocytes, promoted oxidative stress (accumulation of reactive oxygen species), and enhanced lipid peroxidation (elevated thiobarbituric acid-reactive substances), ultimately leading to hepatic fat accumulation[13]. Additionally, *K. pneumoniae* disrupted the intestinal barrier by downregulating tight junction proteins [Occludin and occlusion band 1 (ZO-1)], further contributing to the progression of NAFLD. *Escherichia coli* (*E. coli*) downregulated the Wnt/β-catenin signaling pathway, disrupted the gut-vascular barrier, and damaged the intestinal epithelial barrier[14],

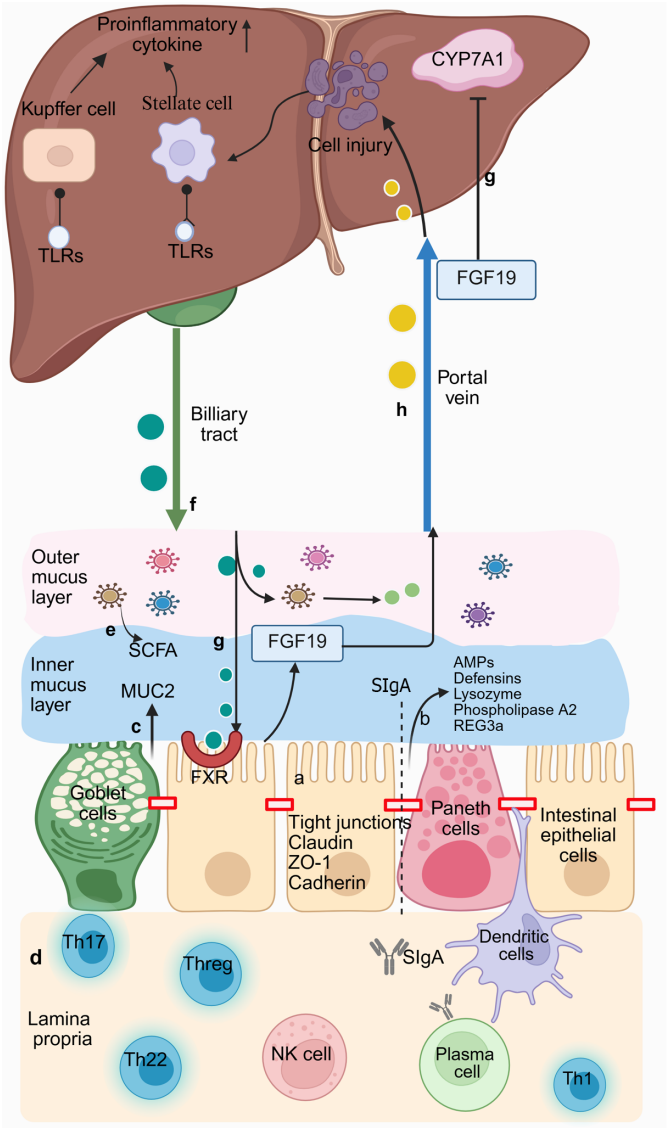

Figure 2 Bidirectional communication between the intestine and liver. a: Intestinal epithelial cells are tightly connected to adjacent cells through apical ligand proteins to seal the intercellular space between them; b: Paneth cells can secrete a range of antimicrobial peptides (AMPs); c: Goblet cells can produce mucin 2 that is made of the mucus barrier. The mucus barrier comprises two layers: An inner dense layer (in blue) close to the epithelial cells, where the inner mucus is almost sterile because of AMPs, and a loose outer layer (in pink) colonized by intestinal microbiota; d: The lamina propria is rich in immune cells. Dendritic cells can capture luminal bacteria and antigens by inserting dendrites between tight junctions. Plasma cells can promote the secretion of dimer IgA. Secretory immunoglobulin A is transported through epithelial cells to the intestinal lumen, where it can limit the colonization and proliferation of potential pathogens; e: Short-chain fatty acids, a major metabolite of intestinal microbiota, can maintain the integrity of the intestinal barrier; f: The liver secretes primary bile acids (BAs) through the biliary duct into the intestinal lumen. Then, colonic bacteria partially convert them into secondary BAs; g: BAs can induce the transcription of fibroblast growth factor 19 (FGF19) by binding to the farnesoid X receptor of enterocytes in the intestine. Then, FGF19 reaches the liver *via* the portal vein. It can downregulate the synthesis of new BAs by inhibiting cholesterol 7a-hydroxylase in hepatocytes; h: Microbe-associated molecular patterns, the metabolites of intestinal microbiota, enter the liver through the portals vein and activate Toll-like receptors (TLRs) on Kupffer and hepatic stellate cells when the cells are damaged. Activated TLRs promote the upregulation of downstream pro-inflammatory cytokines. CYP7A1: Cholesterol 7a-hydroxylase; FGF19: Fibroblast growth factor 19; FXR: Farnesoid X receptor; MUC2: Mucin 2; REG3α: Recombinant regenerating islet-derived protein 3 alpha; SCFA: Short-chain fatty acids; SIgA: Secretory immunoglobulin A; TLR: Toll-like receptor; ZO-1: Occlusion band 1. Created with BioRender (Supplementary material).

thereby promoting bacterial and MAMP translocation and triggering inflammation. Furthermore, through the TLR5/MYD88/NF-κB pathway, *E. coli* activated the transcription factor TWIST1, which induced endothelial-to-mesenchymal transition in liver sinusoidal endothelial cells. These cells subsequently secreted pro-fibrotic factors, exacerbating hepatic stellate cell activation and collagen deposition[15]. In addition, *Streptococcus salivarius* and *Streptococcus vestibularis*, both urease-producing bacteria, degraded urea to produce ammonia and endotoxins. Hyperammonemia crossed the blood-brain barrier, led to astrocyte swelling, and triggered hepatic encephalopathy (HE)[16]. Thus, intestinal microbiota dysbiosis promoted the progression of liver inflammation and fibrosis. As a therapeutic strategy, FMT was successfully applied to improve the composition and metabolic function of the intestinal microbiota, offering a promising treatment for various liver diseases.

FMT AND NAFLD/MASLD

NAFLD is a major cause of chronic liver disease worldwide and represents the hepatic manifestation of metabolic syndrome, primarily characterized by intrahepatocellular triglyceride accumulation. Approximately 20% of patients with NAFLD progress to nonalcoholic steatohepatitis (NASH), a more severe phenotype marked by hepatic inflammation and hepatocyte death[17]. Le Roy *et al*[18] demonstrated that FMT from NAFLD model mice to germ-free recipients induced hepatic steatosis, increased hepatic triglyceride levels, and promoted de novo lipogenesis, highlighting the pivotal role of the intestinal microbiota in NAFLD pathogenesis. Similarly, microbiota derived from obese individuals induced hepatic steatosis in germ-free mice by altering the transcriptional profile of lipid metabolism genes[19]. These findings underscore the role of gut microbiota alterations in driving NAFLD progression. FMT from healthy donors may help correct dysbiosis and thereby offer therapeutic benefits in NAFLD.

Zhou *et al*[20] applied FMT to a mouse model of steatohepatitis. FMT corrected high-fat diet-induced intestinal microbiota dysbiosis by increasing the abundance of beneficial bacteria such as *Christensenellaceae* and *Lactobacillus*. It also upregulated the expression of ZO-1, an intestinal tight junction protein, thereby improving intestinal permeability and alleviating endotoxemia. Typical histological features of NAFLD, such as intrahepatocellular lipid accumulation, were significantly improved, indicating that FMT mitigated high-fat diet-induced metabolic disorders. In a rat model of NASH, García-Lezana *et al*[21] found that heterologous FMT (hFMT) improved intestinal microbiota health-evidenced by restored microbial α-diversity, a shift in composition toward that of healthy controls (with decreased Firmicutes and increased Bacteroidetes), and elevated levels of *Clostridium* and *Adlercreutzia*, which negatively correlated with portal pressure-and normalized portal hypertension. These animal studies encouraged further investigation of FMT for managing liver disease (Table 1). A randomized controlled trial demonstrated that NAFLD patients receiving FMT from vegetarian donors exhibited altered intestinal microbiota composition, an increase in beneficial SCFA-producing bacteria (*Ruminococcus*, *Eubacterium hallii*, and *Faecalibacterium*), lower histological necroinflammation scores (NAFLD activity score), and reduced expression of genes related to liver inflammation and lipid metabolism (ARHGAP18 and serine dehydratase) compared to those receiving autologous FMT[22]. These findings suggest that FMT may improve outcomes in NASH progression and cirrhosis. Craven *et al*[23] also confirmed that hFMT significantly reduced small intestinal permeability in NAFLD patients, enhancing intestinal barrier function. Recently, Xue *et al*[24] evaluated oral probiotics and FMT in NAFLD patients, showing that FMT improved intestinal dysbiosis by increasing SCFA-producing bacteria such as (*Eubacterium*) *coprostanoligenes* group, (*Eubacterium*) *ruminantium* group, *Prevotella* 2, and *uncultured Roseburia spp.*, while reducing pro-inflammatory taxa including the (*Ruminococcus*) *gnavus* group and *Escherichia-Shigella*. FMT also significantly reduced hepatic fat deposition, as evidenced by decreased FibroScan liver fat attenuation values. Notably, FMT was more effective in restoring the intestinal microbiota in lean NAFLD patients than in obese ones. In conclusion, by restoring microbiota balance, FMT may reduce hepatic lipid deposition and inflammation, and decrease portal hypertension and intestinal permeability in NAFLD patients. Currently, six registered clinical trials (Table 2) are investigating the potential benefits of FMT on hepatic steatosis.

FMT AND ALD

Alcohol abuse remains a global health concern, with alcohol-related deaths accounting for nearly 90% of liver disease mortality in some countries[25]. ALD involves extensive liver damage and metabolomic alterations caused by excessive alcohol consumption, with severe alcoholic hepatitis (SAH) representing its most critical form. SAH carries a high short-term mortality rate of 13%-30% within 28 days and a one-year mortality or liver transplantation rate approaching 60%. Current treatments for SAH are limited. Although glucocorticoids reduce 28-day mortality in some patients, their long-term benefits remain unclear, and some patients are intolerant to them[26]. Therefore, novel therapeutic options are urgently needed. Research suggests that the severity of liver damage in ALD is strongly influenced by alcohol-induced intestinal microbiota dysbiosis[27], making FMT a promising strategy for SAH.

In 2016, Llopis *et al*[11] demonstrated that mice transplanted with feces from a patient with SAH developed liver damage after alcohol feeding. In contrast, mice receiving microbiota from a patient with alcoholism but without alcoholic hepatitis showed partial improvement in alanine aminotransferase levels, liver steatosis, and inflammation scores despite continued alcohol exposure. This indicated that FMT could mitigate alcohol-induced liver injury by restoring intestinal microbiota balance, even without alcohol cessation. In 2017, another study confirmed distinct intestinal microbiota profiles in alcohol-sensitive *vs* alcohol-tolerant mice[28]. Transplanting feces from alcohol-tolerant to alcohol-sensitive mice three times weekly normalized the latter's microbiota composition, transaminase levels, and liver inflammatory markers to resemble those of the tolerant donors. Furthermore, the number of mucin-producing goblet cells and the expression of AMPs increased, suggesting that FMT modified the microbiota and inhibited ALD progression. More recently, FMT was found to reduce ethanol acceptance, intake, and preference in a mouse model of alcohol use disorder[29], implying potential benefits in early-stage ALD. Overall, FMT has advanced significantly in managing ALD patients in recent years (Table 1).

Philips *et al*[30] conducted extensive clinical research on SAH. The first clinical report of FMT in SAH was published in 2017. A corticosteroid-resistant SAH patient received daily FMT for 7 days, resulting in changes in intestinal microbiota composition and improvements in HE, bilirubin levels, coagulation markers, and model for end-stage liver disease (MELD) scores. Notably, these improvements persisted for one month. Later that year, Philips *et al*[31] conducted a prospective clinical trial involving eight steroid-ineligible SAH patients who received FMT *via* a nasoduodenal tube for 7 consecutive days. The FMT group showed significant microbiota changes (decreased pathogenic bacteria, such as *K.*

Table 1 Clinical trials and animal studies on fecal microbiota transplantation for chronic liver disease treatment

Disease	Ref.	Year	Type	Comparison	Frequency	Key findings
MASLD/NAFLD	Zhou *et al*[20]	2017	Mice	Control *vs* HFD *vs* HFD + FMT	8 consecutive weeks	FMT mitigated HFD-induced steatohep-atitis through its beneficial effects on intestinal microbiota
	García-Lezana *et al*[21]	2018	Rat	Autologous FMT *vs* allogenic FMT	Once	Allogeneic FMT led to a significant decrease in portal vein pressure
	Witjes *et al*[22]	2020	Human	Autologous FMT *vs* lean vegan donor FMT	3 times within eight weeks	After allogeneic FMT, the expression of hepatic genes related to lipid metabolism and inflammation was significantly reduced. The observed changes in intestinal microbiota composition were found to be connected to changes in plasma metabolites and markers
	Craven *et al*[23]	2020	Human	Autologous FMT *vs* allogenic FMT	Once	Patients who received allogeneic FMT showed a significant reduction in intestinal permeability after 6 weeks
	Xue *et al*[24]	2022	Human	Oral probiotics *vs* FMT + three enemas	Once	FMT effectively improved the therapeutic outcomes in NAFLD patients. It demonstrated greater efficacy in lean NAFLD patients than those with obesity
ALD	Llopis *et al*[11]	2016	Mice	SAH FMT *vs* alcoholism FMT	Once	Transplanting intestinal microbiota from mice with alcoholism, but without AH, alleviated alcohol-induced liver injury
	Ferrere *et al*[28]	2017	Mice	Pectin *vs* FMT	One per week	Manipulating the intestinal microbiota can prevent alcohol-induced liver injury, positioning it as a new therapeutic target for ALD
	Wolstenholme *et al*[29]	2022	Mice	Placebo *vs* FMT	Once	Mice in the FMT group reduced ethanol acceptance, intake, and preference
	Philips *et al*[30]	2017	Human	Case report	7 consecutive days	After FMT, clinical indicators, biochemical markers, and severity scores improved in SAH patients, with significant changes in intestinal microbiota observed
	Philips *et al*[31]	2017	Human	Control *vs* FMT	7 consecutive days	After FMT, there was a improvement in liver disease severity, an increase in survival rates, and notable changes in the composition of the intestinal microbiota
	Philips *et al*[32]	2018	Human	Corticosteroids *vs* nutrition *vs* pentoxi-fylline *vs* FMT	7 consecutive days	FMT showed a higher survival rate compared to other treatments for SAH, potentially serving as a cost-effective bridge to liver transplantation or improving survival without it
	Philips *et al*[33]	2022	Human	Pentoxifylline *vs* FMT	7 consecutive days	FMT improves 6-month survival and reduces liver-related complications, related to beneficial modulation of the gut microbiota
	Philips *et al*[34]	2022	Human	SOC *vs* FMT	7 consecutive days	FMT significantly reduces ascites, infections, encephalopathy, and alcohol relapse, with a trend toward higher survival, associated with beneficial modulation of the gut microbiota
	Sharma *et al*[35]	2022	Human	SOC *vs* FMT	Once	FMT is safe and could improve short- and medium-term survival rates, and clinical severity scores in patients with SAH-ACLF
	Pande *et al*[36]	2023	Human	Prednisolone *vs* FMT	28 consecutive days	FMT is safe, improves 90-day survival, and reduces infections by positively modulating microbial communities
CHB	Ren *et al*[39]	2017	Human	Antiviral therapy *vs* antiviral therapy + FMT	Once every 4 weeks, until HBeAg clearance was achieved	In patients with sustained positive HBeAg after long-term antiviral therapy, FMT can reduce or even eliminate HBeAg levels
	Chauhan *et al*[40]	2021	Human	Antiviral therapy *vs* antiviral therapy + FMT	Once every 4 weeks for a total of six times	FMT is safe and effective in HBeAg clearance in HBeAg-positive CHB patients

PSC	Philips *et al*[43]	2018	Human	Case report	Once a week for a total of four times	After FMT, significant changes were observed in the liver biochemistry, bile acids, and the composition of the intestinal microbiota in PSC patients
	Allegretti *et al*[46]	2019	Human	Control *vs* FMT	Once	The improvement in ALP levels may be linked to an increase in the diversity of the intestinal microbiota, as well as the frequency of FMT
AIH	Liang *et al*[47]	2021	Mice	Control *vs* FMT	28 consecutive days	FMT can alleviate liver injury and bacterial translocation, partially reverse the elevation of serum ALT and AST, restore the balance between follicular regulatory T and helper T cells in the spleen, and effectively correct the intestinal microbiota dysbiosis
Cirrhosis/HE	Wang *et al*[51]	2017	Rat	Control *vs* probiotics *vs* low-dose FMT *vs* moderate-dose FMT *vs* high-dose FMT	3 consecutive weeks	FMT prevents liver necrosis, improves behavioral performance, HE scores, and spatial learning ability in rats, enhances the expression of intestinal tight junction proteins, and repairs intestinal mucosal barrier damage. It also reduces the expression of TLR4 and TLR9 in the liver, along with a decrease in circulating pro-inflammatory factors (IL-1β, IL-6, TNF)
	Kao *et al*[52]	2016	Human	Case report	Once a week for 5 times	FMT can reverse intestinal microbiota dysbiosis and lead to the obvious improvement of cognitive function in dominant HE
	Bajaj *et al*[53]	2017	Human	SOC *vs* FMT + SOC	Once	FMT can reduce the hospitalization rate, improve cognitive function, and restore intestinal microbiota dysbiosis
	Bajaj *et al*[54]	2019	Human	SOC *vs* FMT + SOC	Once	Follow-up for more than one year demonstrated that the positive effects of FMT may be long-lasting
	Bajaj *et al*[55]	2019	Human	Placebo capsules *vs* FMT capsules	15 capsules	Oral FMT capsules are safe and well-tolerated. FMT is associated with improvements in duodenal mucosal diversity, intestinal microbiota dysbiosis, and AMP expression, along with a decrease in LBP levels and better performance in the brain App test
	Bajaj *et al*[56]	2019	Human	Placebo capsules *vs* FMT capsules	15 capsules	FMT has a beneficial effect on the intestinal microbiome function in patients with cirrhosis, leading to improvements in inflammation and cognitive performance. However, recipients with lower levels of secondary bile acids may experience poorer outcomes
	Bloom *et al*[57]	2022	Human	Case report	5 doses of 15 capsules within 3 weeks	FMT capsules improved cognitive performance in patients with HE, with the effect varying based on both donor and recipient factors
	Mehta *et al*[59]	2018	Human	Case report	Once	FMT can significantly reduce arterial ammonia concentrations, alleviate neurological symptoms, and lower CTP and MELD scores in patients with HE
	Li *et al*[60]	2022	Human	Case report	3 times	FMT can improve liver function, relieve clinical symptoms, and significantly reduce the number of HE episodes in patients
	Huang *et al*[61]	2021	Rat	Sham operation *vs* BDL *vs* BDL + FMT *vs* BDL + GMT	5 consecutive days	FMT increased the abundance of *Bifidobacterium* and significantly reduced portal vein pressure
	Bajaj *et al*[62]	2018	Human	SOC *vs* SOC + antibiotic + FMT	Once	FMT has also been shown to restore the diversity and function of the intestinal microbiota altered by antibiotics in patients with advanced cirrhosis who are treated with lactulose and rifaximin

ACLF: Acute on chronic liver failure; AH: Alcoholic hepatitis; AIH: Autoimmune hepatitis; ALD: Alcohol liver disease; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMPs: Antimicrobial peptides; AST: Aspartate aminotransferase; BDL: Bile duct ligation; CHB: Chronic hepatitis B; CTP: Child-Turcotte-Pugh; FMT: Fecal microbiota transplantation; GMT: Transplantation of gut content from the terminal ileum; HBeAg: Hepatitis B e antigen; HE: Hepatic encephalopathy; HFD: High-fat diet; LBP: Lipopolysaccharide-binding protein; MASLD: Metabolic dysfunction-associate steatotic liver disease; MELD: Model for end-stage liver disease; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; PSC: Primary sclerosing cholangitis; SAH: Severe alcoholic hepatitis; SOC: Standard of care; TLRs: Toll-like receptors; TNF: Tumor necrosis factor.

pneumoniae, and increased beneficial bacteria, including *Enterococcus villorum*, *Bifidobacterium longum*, and *Megasphaera elsdenii*), reduced bilirubin and MELD scores, and improved 1-year survival.

In a subsequent retrospective comparison, the FMT group had a lower mortality risk (1 *vs* 2.5, 2.8, and 2.82 for corticosteroid, pentoxifylline, and nutrition groups) and a higher 3-month survival rate (75% *vs* 38%, 30%, and 29%)[32]. Pentoxifylline, a non-selective phosphodiesterase inhibitor with anti-inflammatory and hemorheologic properties, is commonly used in SAH treatment when corticosteroids are contraindicated. The FMT group also exhibited a reduced incidence of HE. Changes in microbiota composition-such as increased *Parabacteroides*, *Porphyromonas*, *Roseburia*, and *Micrococcus*, decreased *Klebsiella*, *Bilophila*, *Citrobacter*, and *Enterobacter*, and colonization by *Lentisphaerae* and *Roseburia*-were associated with improvements in metabolic disturbances, infections, inflammation, and oxidative stress, suggesting a direct link between FMT and clinical outcomes. Philips *et al*[33] retrospectively compared FMT and pentoxifylline in SAH patients. Administered *via* a nasoduodenal tube for 7 days, FMT improved 6-month survival and reduced liver disease complications, including ascites, HE, and severe infections. These benefits correlated with increased *Bifidobacterium* abundance. Subsequently, Philips *et al*[34] evaluated the long-term effects of FMT in SAH patients over three years. FMT significantly reduced ascites, infections, HE, and alcohol relapse while improving survival rates. These benefits were associated with gut microbiota changes, including increased *Bifidobacterium* and reduced *Acinetobacter*.

Another researcher conducted a randomized controlled trial demonstrating the benefits of FMT in SAH patients with acute-on-chronic liver failure[35]. The FMT group exhibited higher survival rates, improved HE remission, and significantly reduced IL-1β levels compared to the standard of care (SOC) group at day 28. At day 90, the FMT group showed better survival and ascites remission rates. Importantly, the incidence of adverse events, such as gastrointestinal bleeding and spontaneous bacterial peritonitis, was similar between groups. Pande *et al*[36] also found that in SAH patients, FMT administered daily *via* nasoduodenal tube for 7 days resulted in higher 90-day survival and lower infection rates compared to the prednisolone group. This was attributed to beneficial modulation of the gut microbiota, including reductions in pathogenic taxa such as *Campylobacter* and potentially harmful anaerobic taxa (*Parcubacteria*, *Weissella*, and *Leuconostocaceae*), alongside increases in taxa such as *Alphaproteobacteria* and *Thaumarchaeota*. These findings suggest that FMT is a safe and effective treatment for SAH, offering a potentially life-saving option for patients with limited therapeutic choices. Ongoing clinical trials are evaluating FMT's impact on alcohol consumption, microbiota dysbiosis, and overall survival in alcohol-dependent patients or those with AH (Table 2).

FMT AND CHRONIC HEPATITIS B

Hepatitis B virus infection remains a significant global public health concern. Patients with chronic hepatitis B (CHB) face an increased risk of cirrhosis and hepatocellular carcinoma (HCC), especially those with persistent hepatitis B e antigen (HBeAg) positivity and active viral replication[37]. Current antiviral therapies primarily target HBV replication; however, their impact on HBeAg seroconversion is limited. Despite prolonged treatment, only a small proportion of patients achieve HBeAg clearance or seroconversion.

The intestinal microbiota plays a crucial role in adaptive immunity and pathogen clearance during HBV infection[38]. Ren *et al*[39] conducted a case-control study involving CHB patients on long-term antiviral therapy (> 3 years) who remained HBeAg-positive. Patients were divided into two groups: One receiving antiviral therapy alone and the other combined with FMT. Sequencing revealed significant microbiota compositional changes post-FMT, including increased *Bacteroides*, *Faecalibacterium*, *Roseburia*, and *Bifidobacterium*; decreased *Klebsiella*, *Escherichia/Shigella*, and *Fusobacterium*; and colonization by *Dialister*, *Fusicatenibacter*, and *Blautia*. These changes were accompanied by a progressive reduction in HBeAg titers after each FMT, with 80% of patients achieving HBeAg clearance. These findings suggest FMT may accelerate HBV clearance. Similarly, a controlled clinical study by Chauhan *et al*[40] in CHB patients remaining HBeAg-positive after more than one year of antiviral therapy reported that FMT combined with antivirals led to higher HBeAg seroconversion rates (16.7% *vs* 0%). Adverse events were mostly mild, including one case of severe abdominal pain resolving within 6 hours, indicating FMT was safe and well tolerated. However, no studies reported HBsAg clearance, underscoring the need for further investigation into FMT's role in HBsAg seroconversion. Currently, three ongoing clinical trials are assessing FMT's effects on HBeAg levels, fibrosis, and survival in HBV-related cirrhosis but have yet to address HBsAg reduction (Table 2).

FMT AND AUTOIMMUNE LIVER DISEASE

Autoimmune liver diseases, including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlap syndrome, arise from immune system dysfunction. Treatment options remain limited;

Table 2 Ongoing clinical trials of fecal microbiota transplantation in chronic liver diseases from Clinicaltrial.gov

Disease or condition	Study title	Study arms	Intervention	Primary outcomes measures	Clinical trials ID, country
NAFLD, NASH	Fecal microbiota transplantation for the treatment of non-alcoholic steatohepatitis	Lean healthy donor frozen FMT		Efficacy (histological resolution of NASH defined as ballooning disappearance with or without persistence of minimal lobulillar inflammation and no progression of fibrosis stage) (time frame: 72 weeks)	NCT03803540, Spain
NAFLD	Effects of fecal microbiota transplantation on weight in obese patients with non-alcoholic fatty liver disease	Diet + exercise + FMT *vs* diet + exercise	3 times IMT with 15-day intervals	Proportion of patients achieving ≤ 5% of the weight loss in kg from baseline (time frame: 3 months)	NCT04594954, India
NAFLD	Dietary counseling coupled with FMT in the treatment of obesity and NAFLD-the DIFTOB study	Healthy diet counseling + FMT *vs* healthy diet counseling + placebo		A change in HOMA-IR (time frame: At week 12 and at week 52)	NCT05607745, Finland
NAFLD with history of diabetes melitus	A prospective, randomized, placebo-controlled pilot study to characterize the intestinal microbiome and to evaluate the safety and fecal microbiome changes following administration of lyophilized PRIM-DJ2727 or placebo given orally for 12 weeks in subjects with NAFLD	Oral PRIM-DJ2727 *vs* oral placebo	twice weekly for 12 weeks	Microbiome diversity in fecal samples as indicated by the Shannon diversity index (time frame: 10 months)	NCT04371653
NASH	Evaluate the efficacy, safety and tolerability of fecal microbiota transfer for the treatment of patients with nonalcoholic steato-hepatitis	Capsules of FMT *vs* capsules of placebo	An initial dose of 24 oral capsules and a maintenance dose of 12 oral capsules every 3 months for 12 months	Proportion of patients with improvement of fat fraction by proton density by MRI and no worsening of activity or fibrosis (time frame: 72 weeks)	NCT05622526
NASH	Fecal microbiota therapy versus standard therapy in NASH related cirrhosis	FMT *vs* standard treatment care	Once a month for 5 months	Reduction in hepatic venous pressure gradient in the two groups from baseline (time frame: 1 year)	NCT02721264, India
Alcohol-related liver disease, alcohol use disorder, cirrhosis	Intestinal microbiota transplant in alcohol-associated chronic liver disease and cirrhosis	IMT capsules *vs* placebo capsules	Twice during the trial	Change in alcohol consumption (time frame: Baseline to 3 months after treatment)	NCT05548452, United States
Liver disease, alcohol dependence, HE and *etc.*	Safety and efficacy of fecal microbiota transplantation	FMT		The efficacy of FMT in treating dysbiosis-associated disorder will be assessed by number of patients who have improvement in clinical symptoms (depends on each disease as stated in outcome) (time frame: 1 year)	NCT04014413, HongKong, China
SAH	A comparison of fecal microbiota transplantation and steroid therapy in patients with severe alcoholic hepatitis	FMT *vs* steroids	7 days	Proportion of participants with overall survival at 3 months (time frame: 3 months)	NCT03091010, India
SAH	Fecal microbiota transplantation in severe alcoholic hepatitis-assessment of impact on prognosis and short-term outcome	FMT *vs* standard of care treatment	1 time	Survival (time frame: 3 months)	NCT03827772, India
AH	Fecal microbiota therapy in steroid ineligible alcoholic hepatitis	FMT *vs* standard medical treatment	7 times	Mortality at 3 months (time frame: 3 months), liver transplant free survival (time frame: 3 months)	NCT05285592, India
AH	Safety evaluation of fecal microbiota transplantation in severe alcoholic hepatitis	Standard of care + oral PRIM-DJ2727 *vs* oral placebo	Every day for a week followed by once weekly for 3 weeks	To assess survival in patients with severe alcoholic hepatitis receiving PRIM-DJ2727 capsules in comparison to standard of care (time frame: Day 1 to 12 months)	NCT05006430, United States
CHB	Study on effect of intestinal	IMT + antiviral	6 times IMT with 2-	Change of serum HBeAg level	NCT03429439,

	microbiota transplantation in chronic hepatitis B	therapy *vs* antiviral therapy	week intervals	(Time Frame: 1 month, 3 months, 6 months)	China
HBV induced cirrhosis	Study on effect of intestinal microbiota transplantation in hepatitis B virus induced cirrhosis	Intestinal microbiota transplantation	4 times IMT with 2-week intervals	Change of liver Fibroscan score (time frame: 3 months, 6 months, 12 months)	NCT03437876, China
Acute-on-chronic liver failure, hepatitis B	Efficacy of addition of FMT and plasma exchange to tenofovir in comparison to monotherapy with tenofovir in ACLF-HBV	Plasma exchange + tenofovir + FMT *vs* tenofovir	7 days	Overall survival in both groups (time frame: Day 28)	NCT04431375, India
Decompensated cirrhosis	Fecal microbiota transplantation for decompensated cirrhosis	FMT + traditional treatment *vs* traditional treatment		Number of adverse events complication rate in all patients in both groups (time frame: 3 months)	NCT03014505, Chian
Cirrhosis, liver	Fecal microbiota transplantation in cirrhosis	FMT *vs* control		Blood ammonia, ALT, AST, gut microbiome, albumin, blood glucose, serum creatinine, direct bilirubin, indirect bilirubin, prothrombin time activity percentage and liver stiffness (time frame: Change from baseline, at 12 months)	NCT04591522
Cirrhosis of the liver	Trial of faecal microbiota transplantation in cirrhosis	FMT *vs* placebo		Assessment of the feasibility of FMT (time frame: 18 months)	NCT02862249, United Kingdom
Liver cirrhosis	Faecal microbiota transplantation for liver cirrhosis	FMT *vs* placebo	3 times	Time to death or readmission due to episode of acute decompensation in FMT treated *vs* placebo treated patients (Time Frame: 1 year)	NCT04932577, Denmark
Cirrhosis, HE	FMT in cirrhosis and hepatic encephalopathy	Dual oral and rectal FMT *vs* oral FMT and rectal placebo *vs* oral placebo and rectal FMT *vs* oral and rectal placebo		Adverse events related to FMT (time frame: 6 months), change in microbial diversity in stool (time frame: 6 months)	NCT03796598, United States
HE	Fecal microbiota transplant as treatment of hepatic enceph-alopathy	FMT oral capsules *vs* placebo oral capsule	days 1, 2, 7, 14, and 21	PHES [time frame: Before the first administration of FMT (day 0) and one week after the last administration of FMT (day 28)]	NCT03420482, United States
HE	Efficacy and safety of fecal microbiota transplant for secondary prophylaxis of hepatic encephalopathy	FMT + standard medical therapy *vs* standard medical therapy	3 times	Proportion of patients developing an episode of hepatic encephalopathy within 6 months (time frame: 6 months)	NCT05229289, India

ACLF: Acute on chronic liver failure; AH: Alcoholic hepatitis; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; FMT: Fecal microbiota transplantation; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HE: Hepatic encephalopathy; HOMA-IR: Homeostasis model assessment of Insulin Resistance; MRI: Magnetic resonance imaging; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; PHES: Psychometric Hepatic Encephalopathy Score; SAH: Severe alcoholic hepatitis.

however, given the BA metabolism abnormalities and gut microbiota dysbiosis observed in these patients[41,42], FMT presents a potential therapeutic approach (Table 1).

In 2018, a case report described FMT in a PSC patient with recurrent bacterial cholangitis[43]. Following four weekly endoscopic FMT procedures without antibiotics, the patient experienced significant and sustained improvements in liver function and circulating BAs, which remained stable for one year. Microbiota analysis revealed a decrease in Proteobacteria-a phylum containing many pathogenic taxa-and an increase in Firmicutes, which includes taxa believed to have beneficial effects on immune regulation. The study demonstrated a strong correlation between improvements in liver function and BAs and the compositional and functional changes of the intestinal microbiota. Interestingly, *Veillonella spp.*, commonly associated with inflammation and fibrosis[44,45], increased after FMT, indicating a need for further investigation. In 2019, Allegretti *et al*[46] conducted a prospective clinical trial involving ten PSC patients with inflammatory bowel disease, administering single-donor FMT. Over 24 weeks, microbial diversity and the abundance of engrafting taxa, including SCFA-producing operational taxonomic units, increased. Notably, 30% of patients exhibited a > 50% reduction in alkaline phosphatase levels, which correlated with microbiota diversity. No adverse events were reported. Data regarding FMT in AIH and PBC remain limited. In an AIH mouse model, FMT reduced liver injury, bacterial translocation, and serum liver enzymes, while restoring gut microbiota disrupted by antibiotics[47]. These findings suggest that FMT is safe and potentially effective in autoimmune liver diseases, but further clinical trials are necessary to clarify

its role in immune-mediated liver conditions.

FMT AND CIRRHOSIS OR HE

Cirrhosis, a consequence of chronic liver diseases, causes extensive liver damage. HE is a serious complication of cirrhosis, for which the current SOC includes oral lactulose and rifaximin. However, over 50% of patients with decompensated cirrhosis experience recurrent or persistent HE despite SOC[48]. Intestinal microbiota disturbances are closely associated with the pathogenesis of both cirrhosis and HE[49,50], positioning FMT as a promising therapeutic option.

In a rat model of HE, FMT reduced intestinal ammonia production, improved liver function, decreased HE severity, and enhanced cognitive functions including behavior, learning, and memory[51]. Moreover, FMT prevented hepatic necrosis and reinforced the intestinal mucus barrier. It also attenuated systemic inflammation by downregulating hepatocyte expression of TLR4 and TLR9 and significantly reducing pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These results support the potential role of FMT in treating cirrhosis and HE (Table 1).

As early as 2016, a case report described FMT for treating HE, demonstrating improvements in cognitive function, reaction time, blood ammonia levels, and quality of life in a patient with mild HE after five weeks of weekly FMT[52]. Although the benefits were temporary after cessation of FMT, it was considered a viable treatment option. Subsequently, Bajaj *et al*[53] conducted several studies on the efficacy and safety of FMT in HE patients. In a 2017 randomized clinical trial, FMT retention enemas combined with SOC outperformed SOC alone, using a single donor enriched in *Lachnospiraceae* and *Ruminococcaceae*. The FMT group exhibited significantly lower rehospitalization rates (0% *vs* 60%), fewer serious adverse events (20% *vs* 80%), improved cognitive function, and increased abundance of beneficial bacteria such as *Ruminococcaceae*. Remarkably, these benefits persisted for over one year during follow-up[54].

In a Phase I trial, Bajaj *et al*[55] administered oral FMT capsules from the same donor. The FMT group showed increased microbial diversity in the duodenum, with higher levels of beneficial bacteria (*Ruminococcaceae* and *Bifidobacteriaceae*) and reduced pathogenic bacteria (*Streptococcaceae* and *Veillonellaceae*) in both the sigmoid colon and feces. Patients also demonstrated improved cognitive performance, elevated expression of duodenal AMPs (E-cadherin and defensin A5), and reduced inflammatory markers such as IL-6 and LPS-binding protein. These effects were confirmed as attributable to FMT rather than placebo in a subsequent study[56]. Compared to baseline, patients exhibited higher levels of deconjugated and secondary BAs, with beneficial microbiota linked to improved cognition and reduced inflammation, including *Ruminococcaceae*, *Verrucomicrobiaceae*, and *Lachnospiraceae*. FMT was well tolerated with few serious adverse events reported. These findings indicate that FMT can enhance cognitive function and intestinal barrier integrity while reducing systemic inflammation in HE patients, with minimal adverse effects.

Unlike Bajaj *et al*[56], who used a single donor, Bloom *et al*[57] administered FMT from five donors to 10 patients to assess its safety and efficacy in HE. Results showed that although HE recurrence rates decreased and cognitive function improved, outcomes varied depending on donor and recipient. Responders had baseline and sustained enrichment of *Bifidobacterium* and other beneficial microbiota, while donors with the lowest SCFA levels were linked to poorer cognitive outcomes in recipients. This suggests that FMT effectiveness may depend on the relative abundance of beneficial bacteria in donors. One patient developed extended-spectrum β-lactamase (ESBL)-producing *E. coli* bacteremia 17 days after the last FMT, presenting with fever, cough, and infiltrative shadow on chest radiograph[58]. Gram-negative rod bacteria (later confirmed as ESBL-producing *E. coli*) were detected in blood culture. Despite initial levofloxacin treatment, infection was controlled only after a 14-day carbapenem course, and the patient stabilized. This infection was later traced back to the FMT donor capsules, as detailed further in the manuscript.

Mehta *et al*[59] studied FMT in 10 HE patients and reported significant reductions in arterial ammonia, neurological symptoms, and Child-Turcotte-Pugh and MELD scores after FMT. Li *et al*[60] also evaluated FMT effectiveness in two hepatitis B cirrhosis patients with recurrent HE following transjugular intrahepatic portosystemic shunt. After three FMT sessions *via* gastroscopy, both patients demonstrated improved liver function, relieved clinical symptoms, reduced Child-Pugh scores, fewer HE episodes, and improved gut microbiota composition. No FMT-related adverse events occurred, except for temporary constipation in one patient. In addition, Huang *et al*[61] induced a cirrhosis-related portal hypertension model using bile duct ligation and showed that FMT increased Bifidobacterium abundance and significantly reduced portal vein pressure. This effect was attributed to improvements in mesenteric hyperdynamic circulation and vasodilation, decreased mesenteric angiogenesis, and alleviated splenorenal shunting. These findings suggested that the therapeutic benefits of FMT were not mediated by reducing hepatic fibrosis or intrahepatic vascular resistance but by modulating extrahepatic hemodynamics-specifically by improving systemic hyperdynamic circulation, inhibiting pathological vasodilation and angiogenesis, and reducing portosystemic collateral formation. Antibiotic use is common in cirrhosis patients and reduces microbiota diversity and native taxa abundance. FMT restored this diversity (increased Chao1 index, higher abundance of *Lachnospiraceae* and *Ruminococcaceae*), enhanced SCFA secretion, regulated BAs (restored secondary BA levels), improved cognitive function, and lowered readmission rates for recurrent HE[62].

Clinical data suggested that FMT targeted intestinal dysbiosis in cirrhosis and HE by restoring intestinal barrier integrity and reducing ammonia absorption, which significantly lowered relapse and readmission rates while improving cognitive function. These encouraging results showed that most recipients experienced no severe FMT-related adverse effects. Seven ongoing clinical trials (Table 2) were evaluating the impact of FMT on blood ammonia, liver function, HE relapse, and readmission rates in cirrhosis and HE patients.

POTENTIAL APPLICATIONS OF FMT

Given FMT's capacity to restore gut microbiota balance, repair intestinal barrier function, enhance the abundance of SCFA-producing bacteria, upregulate AMP expression, and downregulate hepatic TLR expression, it may help alleviate systemic inflammation and restore immune homeostasis. These mechanisms, along with encouraging results in decompensated cirrhosis and acute-on-chronic liver failure, suggested that FMT could be a promising therapeutic strategy to improve outcomes in patients with acute decompensation of cirrhosis.

Additionally, HCC, the terminal stage of various liver diseases, is characterized by intestinal microbiota dysbiosis that compromises antitumor immune surveillance and promotes HCC development[63]. Although FMT has not yet been applied in HCC patients, it has been studied in patients and animal models with other malignancies[64-67]. These studies indicated that FMT enhanced the antitumor effects of anti-programmed cell death protein 1 therapy, accompanied by changes in intestinal microbiota, suggesting that FMT could serve as an important adjunctive treatment for HCC.

ADVERSE EVENTS, CURRENT CHALLENGES, AND PRACTICAL FUTURE

Intestinal microbiota dysbiosis plays a crucial role in the pathogenesis of various liver diseases. FMT, an emerging strategy to restore healthy intestinal microbiota, has demonstrated promising benefits in managing chronic liver diseases. These benefits included amelioration of liver inflammation, induction of HBeAg clearance, reduction in biochemical markers and disease severity scores, and improvements in lipid metabolism, cognitive function, and overall clinical prognosis. Currently, 22 FMT studies related to liver diseases are registered on ClinicalTrials.gov, focusing on evaluating the effectiveness and safety of FMT. Further research on the role of FMT in liver diseases is anticipated in the coming years.

Safety is a critical consideration, as patients with severe liver disease are often the primary recipients of FMT. Numerous studies reported the safety of FMT across diverse populations, including children, the elderly, cancer patients, immunosuppressed individuals, and critically ill patients[68-71]. In recent studies of FMT for liver diseases, most recipients did not experience serious adverse effects, although some reported transient symptoms such as bloating, diarrhea, or constipation following the procedure[30,60]. Notably, one patient with HE developed ESBL-producing *E. coli* bacteremia after FMT[57], traced to the donor capsules[58].

Alarmingly, FMT capsules from the same donor were administered to a patient undergoing allogeneic hematopoietic-cell transplantation for therapy-related myelodysplastic syndrome, resulting in fever and chills. Blood cultures revealed ESBL-producing *E. coli*, and despite escalation of antibiotic treatment (from cefepime to meropenem), the patient succumbed to severe sepsis. These cases underscore the importance of rigorous donor screening to prevent transmission of potentially infectious pathogens, including ESBL-producing bacteria, which are prevalent in fecal microbiota[72]. Furthermore, one study raised concerns about increased abundance of *Veillonella*, a potentially pathogenic genus with significant implications for infection and immunity, following FMT[43]. Whether this increase is common and if it poses long-term risks requires further investigation. Given the compromised intestinal barrier and immune function in liver disease patients, they are more susceptible to pathogenic microorganisms that may escape routine screening. Besides patients with chronic liver diseases, many FMT candidates are immunocompromised, and safety in this population remains debated. The 2024 American Gastroenterological Association guidelines[73] suggest that traditional FMT may be considered selectively in patients with mild to moderate immunosuppression but is not recommended in cases of severe immunosuppression-such as active chemotherapy, profound neutropenia post-hematopoietic stem cell transplantation, or advanced HIV infection with CD4 counts < 200/mm^3. However, a meta-analysis of 303 immunocompromised patients with *Clostridioides difficile* infection (CDI) showed that serious adverse event rates following FMT were comparable to those in immunocompetent individuals, without increased infection risk, and clinical remission rates were similar[74]. Additionally, Benech *et al*[75] reported no higher incidence of adverse events in certain immunosuppressed subgroups. The potential benefits of FMT, including reducing prolonged antibiotic use, may outweigh risks. Therefore, they recommended individualized, case-by-case assessments when considering FMT in immunocompromised patients. Current guidelines and consensus in multiple countries emphasize strict donor screening and advocate close monitoring of both short- and long-term adverse events in FMT recipients.

Most previous studies focused on a single donor, while Bloom's analysis examined cognitive improvements in HE patients using five distinct FMT donors. Bloom *et al*[57] confirmed that FMT effectiveness varied depending on both donor and recipient factors. This prompted investigation into whether donor fecal microbiota heterogeneity impacts patient outcomes, whether a "super-donor" exists, and the relative influence of donor *vs* recipient on FMT efficacy. A comprehensive study comparing fecal quantitative metagenomics from 316 patients before and after FMT concluded that recipient factors consistently outweighed donor factors in determining FMT outcomes[76]. Notably, the study identified complementarity between donor and recipient intestinal microbiota as the strongest determinant of FMT success. These findings suggest that, in addition to donor health screening, the recipient's intestinal microbiota should be routinely assessed and matched with the donor's microbiota prior to FMT. Furthermore, predictive models have been developed to forecast recipient gut microbiota composition post-FMT[77], guiding donor selection to establish specific, desired microbiota profiles in recipients. This approach could enhance FMT success rates while minimizing adverse effects.

Clinical researchers have recognized the potential of FMT in liver diseases; however, consensus on the most effective implementation strategy has not yet been reached. First, the efficacy of a single FMT was limited in patients with chronic liver disease due to the prolonged duration of liver injury. Studies on FMT in chronic liver disease varied in the number and frequency of administrations, as shown in Tables 1 and 2, and current guidelines lacked standardized recommend-

ations on these parameters. Second, various delivery routes-including enema, colonoscopy, nasogastric tube, nasojejunal tube, and oral capsule-have been used in clinical studies. Among these, colonoscopy was generally considered more effective[78]. However, a recent meta-analysis concluded that combined administration routes (using both upper and lower gastrointestinal approaches) might provide greater efficacy[77]. Third, studies applied differing single and total doses depending on delivery routes and preparation methods. Guidelines recommended no less than 12.5 g of stool for upper gastrointestinal FMT and 25 g for lower gastrointestinal FMT[79]. The study also demonstrated that clinical success closely correlated with microbial engraftment, with a higher microbial load in the stool increasing the likelihood of success[80]. Fourth, consensus has not been reached on whether antibiotic pretreatment of recipients is necessary before FMT. While several recommendations suggested that patients with recurrent CDI (rCDI) receive vancomycin or fidaxomicin for at least 3 days before FMT, with antibiotics discontinued 12-48 hours prior to the procedure[78,81,82], the necessity of antibiotic pretreatment in non-rCDI conditions remained controversial. According to the European FMT Clinical Practice Consensus, insufficient high-quality evidence supported antibiotic pretreatment for conditions other than rCDI[78]. In contrast, based on low-level evidence, a consensus from Nanjing, China suggested that antibiotic pretreatment might benefit patients without bacterial infections before FMT[81]. Currently, clinical researchers explore antibiotic pretreatment based on individual experience and patient conditions, anticipating future studies to confirm whether this approach enhances FMT efficacy. In conclusion, no unified, standardized protocol exists for FMT regarding delivery routes, dosages, interventions, or antibiotic pretreatment in chronic liver disease. Well-powered follow-up studies are needed to establish the optimal FMT protocol.

CONCLUSION

FMT demonstrated significant therapeutic potential in chronic liver diseases by improving liver inflammation, biomarkers, lipid metabolism, cognitive function, and overall clinical prognosis. However, given the severe liver damage and impaired intestinal barrier function in these patients, rigorous donor screening was essential to ensure safety and efficacy. The optimal FMT protocol remains under refinement, with critical factors-including donor-recipient microbiota compatibility, delivery routes, stool doses, and antibiotic pretreatment-requiring careful consideration. Further research is needed to establish a standardized and effective treatment protocol.

FOOTNOTES

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Country of origin: China

ORCID number: Lei Ma 0009-0009-1098-3948; Meng-Han Zhang 0000-0002-2983-2033; Yi-Fan Xu 0000-0003-2188-0804; Yan-Xu Hao 0000-0002-3317-2875; Xuan-Xuan Niu 0000-0002-7418-2076; Yan Li 0009-0003-9313-4840; Hui-Chun Xing 0000-0002-9111-9669.

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