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REVIEW

Intestinal microbiota pathogenesis and fecal microbiota transplantation for inflammatory bowel disease

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Abstract

The intestinal microbiota plays an important role in inflammatory bowel disease (IBD). The pathogenesis of IBD involves inappropriate ongoing activation of the mucosal immune system driven by abnormal intestinal microbiota in genetically predisposed individuals. However, there are still no definitive microbial pathogens linked to the onset of IBD. The composition and function of the intestinal microbiota and their metabolites are indeed disturbed in IBD patients. The special alterations of gut microbiota associated with IBD remain to be evaluated. The microbial interactions and host-microbe immune interactions are still not clarified. Limitations of present probiotic products in IBD are mainly due to modest clinical efficacy, few available strains and no standardized administration. Fecal microbiota transplantation (FMT) may restore intestinal microbial homeostasis, and preliminary data have shown the clinical efficacy of FMT on refractory IBD or IBD combined with *Clostridium difficile* infection. Additionally, synthetic microbiota transplantation with the defined composition of fecal microbiota is also a promising therapeutic approach for IBD. However, FMT-related barriers, including the mechanism of restoring gut microbiota, standardized donor screening, fecal material preparation and administration, and long-term safety should be resolved. The role of intestinal microbiota and FMT in IBD should be further investigated by metagenomic and metatranscriptomic analyses combined with germ-free/human flora-associated animals and chemostat gut models.

Key words: Inflammatory bowel disease; Intestinal microbiota; Probiotics; Fecal microbiota transplantation; Synthetic microbiota transplantation

Core tip: Several lines of evidence strongly support the link between intestinal microbiota and inflammatory bowel disease (IBD). This review discusses the potential microbial pathogens, disturbance of intestinal microbiota, and immune interactions between host and microbes in IBD. Furthermore, alternative IBD treatment approaches aimed at restoring the disturbed intestinal microbiota have become a major interest in recent years. This article also reviews the present literature concerning the clinical use of probiotics, especially fecal microbiota transplantation and its barriers, and future directions in the management of IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic relapsing nonspecific inflammatory disorder of the gastrointestinal (GI) tract. The etiology of IBD is unknown. Contributing factors to the pathogenesis of IBD include disturbance of the intestinal microbiota and its metabolites, the host's genetic susceptibility, and the host's innate and acquired immunity[1,2]. Many studies based on metagenomics have profiled the normal patterns of the human intestinal commensal microbiota. For example, 3.3 million microbial genes, up to 10 bacterial phyla, and > 1000 bacterial species (> 90% species belong to the phyla *Bacteroidetes* and *Firmicutes*) have been identified in the human intestine[2,3]. Commensal fungi and viruses have also been detected in the human gut[2,4]. Several lines of evidence strongly support the link between intestinal microbiota and IBD such as: (1) animal studies confirm that intestinal microbiota has an essential role in the pathogenesis of IBD, because colitis cannot be induced in germ-free animal models[5,6]; (2) fecal stream diversion prevents recurrence of CD in the neoterminal ileum, but reinfusion of luminal contents into bypassed colonic segments rapidly results in recurrent disease[7,8]; (3) fecal and intestinal mucosa-associated microbiota of IBD patients is characterized by decreased biodiversity and abnormal compositions (*e.g.*, an imbalance between protective and harmful microbes)[2,9]; (4) the disturbed metabolites of intestinal microbiota (*e.g.*, abnormal butyrate metabolism) are implicated in the pathogenesis of IBD[10,11]; (5) several probiotic products may be effective in relieving intestinal symptoms and preventing relapse in UC[12]; (6) some non-absorbable antibiotics may induce and maintain remission in IBD[12,13]; (7) many environmental factors such as the westernized diet, modern lifestyle, or abuse of antibiotics, have an important effect on the composition of intestinal microbiota and contribute to the significant increased incidence of IBD[9,14]; and (8) IBD-related genetic susceptibility loci are mainly associated with the host-microbe immune interactions[15-17].

Previously, researchers have tried to determine the specific microbial pathogens associated with the onset of intestinal inflammation of IBD[18-22]. Recently, metagenomic studies have increased with the development of high-throughput DNA sequencing and bioinformatics analysis technology[2,23,24]. Therefore, many studies have focused on the composition and function of gut microbiota in IBD patients, but the defined alteration of intestinal microbiota, the microbial interactions and host-microbe interactions are still not conclusive[2,9,25]. Furthermore, IBD-related conventional medical treatments use aminosalicylates, steroids, immunosuppressive agents and biological therapies with many adverse effects, and no cure is available. Alternative IBD treatment approaches aimed at restoring the disturbed intestinal microbiota have become a major interest in recent years. Many clinical trials have been performed to investigate the efficacy of probiotics in IBD. The beneficial effect of probiotics is modest, although several probiotic products can induce and maintain remission in UC[26,27]. Recently, fecal microbiota transplantation (FMT) has re-emerged as a hot research topic[28-30], largely due to its efficacy on the management of recurrent *Clostridium difficile* infection (CDI). FMT is now recommended as an alternative to standard therapy with antibiotics for recurrent CDI[31,32]. Importantly, FMT may restore the balance of intestinal microbiota, so it is also proposed as an alternative treatment for IBD[33]. Thus so far, several case series have shown the efficacy of FMT in refractory IBD, and IBD combined with CDI[34-37], but it is not clear whether FMT has potential therapeutic value for IBD patients with mild IBD. FMT clinical application in IBD still leaves many unanswered questions. FMT-related screening of donor, fecal material preparation and administration is not standardized, and the defined microbial restoration mechanisms and long-term safety of FMT are still not clarified[38,39]. Moreover, FMT researchers have to prepare and submit the complex investigational new drug applications in the future[40]. This study reviews the present literature concerning the potential microbial pathogenesis in IBD, particularly FMT and its role in the management of IBD.

Table 1 Possible microbial pathogens associated with inflammatory bowel disease

Mycobacterium avium subspecies *paratuberculosis*[19,126,127]
Adherent-invasive *Escherichia coli*[18,44,45,128]
Clostridium difficile[107,129,130]
Candida albicans[21,49]
Helicobacter sp.[131-133]
Campylobacter sp., such as *Campylobacter jejuni* and *Campylobacter concisus*[134-136]
Salmonella sp.[135]
Klebsiella sp.[137]
Yersinia sp.[138]
Listeria sp.[139]
Fusobacterium sp.[140]
Methanosphaera stadtmanae[141]
Bacteroides fragilis[142]
Norovirus[143]

POTENTIAL MICROBIAL PATHOGENS IN IBD

Many studies have investigated the specific microbial pathogens contributing to the onset of IBD; however, no definitive pathogens have been confirmed[10]. The potential bacterial, fungal or viral pathogens related to IBD are listed in Table 1. *Mycobacterium avium* subspecies *paratuberculosis* can colonize the ileal mucosa of CD patients[19], which has been often linked to the etiology of CD, but with no conclusive evidence to its involvement[41-43]. Moreover, *Escherichia coli* (*E. coli*) strain LF82 was isolated from the ileum of CD patients[18]. Several studies have shown that CD patients have a higher prevalence of adherent-invasive *E. coli* (AIEC) in ileal lesions, which indicates a specific association of AIEC with CD[20,44]; higher expression of the outer membrane porin C of

AIEC can be observed in patients with CD[45]. AIEC proliferation has also been found in the colonic mucosa of UC patients[46]. Although the enhanced adherence and invasion of AIEC is present among IBD patients, the potential mechanisms between AIEC and IBD still need to be clarified. Furthermore, CDI is common among IBD patients, and similar symptoms between CDI and IBD makes it difficult to distinguish between them[47]. CDI can activate the intestinal proinflammatory response and is responsible for the development or exacerbation of IBD. IBD itself may contribute to the increased risk of CDI[47]. However, there is no clear evidence that CDI precedes IBD. Much evidence has shown that fungal pathogens may be involved in the pathogenesis of IBD, especially CD[1]. Anti-*Saccharomyces cerevisiae* antibodies (ASCAs) as one of the serological markers for CD can also be induced by *Candida albicans* (*C. albicans*)[7,48]. *C. albicans* can be isolated from the intestine more frequently in CD patients and their healthy relatives, but the positive association between ASCAs level and the amount of *C. albicans* in CD is still controversial[49,50]. Inhibition of interleukin (IL)-17A by secukinumab is ineffective in active CD patients[51], which may be linked to *C. albicans* thriving in the gut induced by loss of control by IL-17[52]. In addition, large amounts of *Candida* sp. can also be detected in the feces or intestinal mucosa among UC patients[50], and the clinical symptoms and intestinal inflammation may be improved after antifungal treatment. Although many studies have shown a higher prevalence of pathogenic microbes in IBD, no specific pathogenic microbe has been identified to date, and the cause and consequence relationship of the single pathogenic microbe and IBD development is still controversial. Increasing evidence has confirmed that the disturbance of the intestinal microbial community may be responsible for the pathogenesis of IBD.

DISTURBANCE OF INTESTINAL MICROBIOTA IN IBD

With the development of culture-independent techniques such as metagenomic analysis, the disturbance of intestinal microbiota associated with IBD has been better described. This includes the involvement of the feces/colonic mucosa-associated microbiota, inflamed lesions-/normal mucosa-related microbiota[53], and even the intestinal microbiota in IBD remission and relapse[54]. Although the conclusions about the altered intestinal microbiota are still uncertain, more consistently observed alterations of intestinal bacterial microbiota linked to IBD have been reported. The decrease in biodiversity and depletion of the phyla *Bacteroidetes* and *Firmicutes* can be observed in feces/mucosa-associated microbiota among IBD patients[2,55,56]. The bacterial communities in the intestine are significantly different between UC and CD patients and healthy individuals[57,58]. Furthermore, at the genus level, many potentially protective bacteria and normal anaerobic bacteria such as *Bacteroides* sp., *Eubacterium* sp. and *Lactobacillus* sp., are significantly decreased both in active UC and CD patients, and even in patients with inactive IBD[59-68]. In addition, the abnormal metabolites of intestinal bacterial microbiota can also contribute to the pathogenesis of IBD[69,70]. For example, butyric acid, which is the main energy source of the intestinal epithelial cells, can inhibit the signal pathway of proinflammatory cytokines. Butyrate-producing bacteria and their culture supernatants can improve the intestinal inflammation and necrosis in the animal model of colitis[71]. In parallel, some studies have confirmed that the levels of some butyrate-producing bacteria (*e.g.*, *Clostridium* clusters IV and XIVa) and the availability of butyrate reduced significantly in UC patients[11,72]. Moreover, the metabolic activity of intestinal microbiota in UC is disturbed, with increased levels of taurine and cadaverine[73]. Until now, the highly reproducible profiles of intestinal microbiota established for IBD patients have been limited. Recently, one study based on a phylogenetic network analysis showed that the human intestinal mucosal bacterial community could be organized into five preserved microbial modules and two IBD-associated microbial modules displayed enhancement of the oxidative response and glycan metabolism pathways relevant to host-pathogen interactions[25].

The fungal communities are also important components of microbiota in the human GI tract; most of which have co-evolved with the host in a symbiotic relationship[21]. Early studies based on culture-dependent methods reported that fungi were detected in the digestive tract of 70% of healthy adults[74], and the number of fungi in the human colon is 10^2-10^6 cfu/mL; most of which are aerobic or facultatively anaerobic. Recently, metagenomic analysis of 124 individuals reported that only 0.1% of microbial genes in feces were of eukaryotic or viral origin[2], which was consistent with previous reports of intestinal microbiome accounting for 0.03% of the fecal microbiota[75]. There is limited information available about the prevalence and classification of the intestinal fungal microbiota. The study of the fungal microbiota is in its infancy, and much remains to be determined[75]. There were significant differences in fungal communities related to IBD compared to non-IBD controls. The fungal sequences could be detected in the colonic mucosa of all IBD patients, and the diversity of the intestinal microbiome increased clearly among IBD patients, but the proportion of microbiome in the whole intestinal microbiota was low[75]. Moreover, whether the intestinal microbiome interacts with the mucosal immune system or influences intestinal disorders is unknown. Recently, a study connected intestinal fungal microbiota with the host immune system through Dectin-1 in a mice model of dextran-sulfate-sodium-induced colitis[1], which confirmed the fungal etiology in IBD.

Overall, the diversity and abundance of intestinal bacterial microbiota are reduced in IBD, and the bacterial microbiota metabolites are also disturbed. However, a specific IBD microbiota has not yet been revealed, which might in part be because of inter-individual vari-

ability, different IBD characteristics or subtypes, and different data analysis methods. In addition, whether the microbiota pathogenesis is the initiating factor in IBD or is secondary to IBD still cannot be answered. Moreover, further studies based on fungal high-throughput DNA sequencing should be conducted on whether the change of the fungal community structure is secondary to the imbalance of the intestinal bacterial community, or independent pathogenic factors of IBD.

HOST-MICROBE IMMUNE INTERACTIONS IN IBD

The human immune system is usually tolerant of the commensal microbiota colonized in the GI tract. Abnormal activation of the host immune response against the imbalanced intestinal microbiota may be the potential pathogenesis mechanism of IBD[76]. Additionally, an abnormal intestinal microbiota offers persistent stimulation of the immune system in individuals who are genetically susceptible to IBD, which results in dysfunction in immune tolerance and regulation. The resulting chronic intestinal inflammation in the GI tract can initiate intestinal lesions and lead to IBD-associated symptoms. Intestinal mucosal epithelial cells are continuously exposed to the intestinal microbiota, and they can recognize various cell wall components of pathogenic and commensal microbes, which are the main sources of pathogen-associated molecular patterns. The pattern recognition receptors (PRRs) on intestinal cells include Toll-like receptors (TLRs)[77], NOD-like receptors (NLRs) and C-type lectin receptors (CLRs), which are essential for a human host to recognize endogenous/exogenous microbes, and trigger and maintain intestinal mucosal innate and acquired immunity. The immune responses mediated by PRRs on intestinal cells include microbial binding and phagocytosis; induction of antimicrobial effect or mechanisms; and the production of endogenous antimicrobial peptides, cytokines and chemokines. Moreover, the majority of IBD-related genetic susceptibility loci are associated with PRRs. For example, the polymorphisms in NOD2 have been identified to increase the risk of CD in western populations, and the polymorphisms in TLRs are associated with UC and CD. In addition, CLRs such as Dectin-1 can contribute to the recognition of intestinal fungi and influence the immune function of intestinal mucosa in UC[1].

CLINICAL USE OF PROBIOTICS IN IBD

The intestinal dysbiosis in IBD has been confirmed by molecular techniques, and there is a compelling rationale for modulating the altered intestinal microbiota among IBD patients. Animal studies have confirmed that probiotics enhance the intestinal mucosal barrier function, regulate intestinal mucosal immunity, recover intestinal microbial community structure, and improve chronic intestinal inflammation. Clinical trials in humans have investigated whether the present probiotic products could be a treatment option in IBD. Some bacterial strains of *Lactobacillus* sp.[78,79], *Bifidobacterium* sp.[80,81], *Escherichia* sp. (*e.g.*, *E. coli* Nissle 1917)[82,83], and the fungal strain *Saccharomyces boulardii* (*S. boulardii*)[84,85], are the most common investigated probiotics in the treatment of IBD. In addition, except for the single probiotic strain, some probiotic combinations such as VSL#3, an eight probiotic consisting of four strains of *Lactobacillus*, three strains of *Bifidobacterium*, and one strain of *Streptococcus*, have shown efficacy by maintenance of remission both in adults and children with active IBD[86-88].

According to the efficacy of probiotics in UC, patients may experience fewer relapses when probiotics of *Lactobacillus* sp. are added to their usual therapies or when they cannot tolerate standard medications[89]. In addition, *E. coli* Nissle is an effective alternative to aminosalicylates for maintenance of UC remission[82,83]. Administration of *S. boulardii* during maintenance treatment with mesalazine induced clinical remission in 71% of patients with active mild to moderate UC[85]. Moreover, VSL#3 resulted in a combined induction of remission/response rate of 77% among patients with active mild to moderate UC and who did not respond to conventional therapy[87]. Furthermore, the effects of probiotics on pouchitis are by far the most convincing data. VSL#3 is more effective than placebo for prevention and treatment of pouchitis for postoperative UC patients[90]. Overall, a Cochrane review showed that conventional therapy combined with probiotics has few beneficial effects on the induction of remission in active mild to moderate UC, but probiotics may be useful in the maintenance of remission in non-active UC and in the prevention of postoperative recurrence; the outcomes from the present clinical trials on probiotics in UC need to be confirmed. On the other hand, current data show that *S. boulardii* has no beneficial effects on maintaining remission in CD patients[84], but might lead to fewer relapses when combined with mesalamine[91]. Moreover, probiotics of *Lactobacillus* sp. cannot prevent postoperative relapse of CD[78,92]. There is insufficient evidence to draw any conclusions about the efficacy of probiotics for induction or maintenance of CD remission[27]. Importantly, *Faecalibacterium prausnitzii* (*F. prausnitzii*) identified as a butyrate-producing species, may contribute to the gut homeostasis and play a protective role in IBD, especially in CD[71]. The levels of *F. prausnitzii* in feces and intestinal mucosal biopsies decrease both in CD and UC[93-96], and the lower level of *F. prausnitzii* on the ileal mucosa of CD patients is associated with recurrence. However, one study showed an increased level of *F. prausnitizii* in mucosal biopsies associated with reduced bacterial diversity in pediatric CD[97]. Generally, *F. prausnitzii* is a potential and promising probiotic, and its protective role in IBD is worthy of investigation.

In summary, the clinical efficacy of the present probiotic products in the treatment of IBD is modest; they are currently used only as supplements in IBD treatment, and not as alternatives or substitutes for conventional

therapy. The application of probiotics should be based on the principles of evidence-based medicine, but well-designed randomized controlled trials (RCTs) are lacking. Further appropriate study designs and larger numbers of patients will be needed to determine the optimal probiotics for IBD.

INDICATIONS FOR FMT

FMT, also called stool/fecal transplantation or fecal bacteriotherapy, refers to infusion or engraftment of a homogenized fecal suspension from a healthy individual into the GI tract to cure a specific disease[29,32,98]. Due to the elucidation of the composition and function of intestinal microbiota by the development of metagenomics studies, many researchers have begun to explore therapeutic interventions in human diseases associated with intestinal dysbiosis from the viewpoint of microecology. Although various probiotics, prebiotics and synbiotics have been administrated in clinical practice, most are recommended as supplementary treatments due to poor therapeutic effects and the limited number of available strains. So far, only the preliminary application of FMT exhibits marked clinical effectiveness, especially in the treatment of recurrent CDI and IBD[30,33,99,100]. Traditionally, CDI is mainly treated with antibiotics such as vancomycin and metronidazole. However, the therapeutic effect is poor due to the drug resistance of *C. difficile*. The recurrence rate of CDI is much higher, and can be up to 15%-26%[101]. FMT can be considered to replace antibiotics for recurrent and refractory CDI that has relapsed more than three times[31]. A recent RCT about FMT suggested that 81% of recurrent CDI patients achieved remission of symptoms after FMT, while only 31% of patients receiving only vancomycin treatment exhibited symptom remission[102]. A multicenter long-term follow-up study on FMT treatment of recurrent CDI through a colonoscopy route demonstrated a 91% primary cure rate and 98% secondary cure rate[101]. A recent systematic review showed that FMT could achieve clinical remission in 63% of IBD patients, while 76% of the patients could stop taking IBD-related drugs and their GI symptoms were reduced[33]. Several preliminary studies using FMT for GI disorders including irritable bowel syndrome, antibiotic-associated diarrhea and chronic constipation have also met with some success. In addition, non-GI disorders such as diabetes mellitus and insulin resistance[103], metabolic syndrome, childhood autism, chronic fatigue syndrome, multiple sclerosis, fibromyalgia, myoclonus dystonia and Parkinson's disease are reported to be improved and cured with FMT[39,104].

FMT IN THE MANAGEMENT OF IBD

The treatment of IBD is rapidly evolving, and many conventional and novel drug treatments have proven effective, including aminosalicylates, steroids, immunosuppressive agents and biological therapies. However, some patients become refractory to standard management, and some have significant adverse effects, with many patients requiring surgery. Despite medical treatment, a significant number of patients live with mild active symptoms and have a poor quality of life. Given the role of the intestinal microbiota in driving inflammation in IBD, treatments that manipulate the microbiota have been investigated including the use of probiotics and prebiotics, with variable evidence for their efficacy. FMT is becoming an alternative microbiota treatment for IBD with astounding efficacy.

The main case series and case reports of FMT for IBD treatment are shown in Table 2. The first case report of FMT for IBD was published in 1989, in which the author himself confirmed UC for 7 years that was refractory to sulfasalazine and steroids. Six months after transplantation of a healthy donor stool by retention enemas, he remained symptom free[34]. Moreover, a case series of six patients with refractory UC apparently achieved complete, medication-free remission after FMT with no disease recurrence after 1-13 years follow-up[35]. Recently, a system evaluation reported that FMT could achieve clinical remission in 63% of IBD patients, while 76% of patients could stop taking IBD-related drugs and their GI symptoms were reduced[33]. However, a study including five patients with moderate to severe active UC showed that none of them achieved remission after FMT by week 12, and a positive clinical response was observed only in one patient[105]. The poor response in that study may have been associated with the severity of UC itself, rather than the optimal administration of FMT. FMT may be an optimal treatment for refractory IBD with no response to current conventional therapy, such as anti-inflammatory agents, steroids, immunosuppressive and biological drugs. For refractory IBD, continuously repeated FMT is needed to cure or achieve effective remission[38]. However, no unified standard exists in the procedures of FMT treatment in IBD. In addition, CDI is common among IBD patients with an incidence of 3.7%[106]. Once combined with CDI, the severity of IBD can be aggravated, while the recurrence rate of CDI can be increased[107]. There is no standard therapy for UC combined with CDI. For example, vancomycin and metronidazole would be preferred but with poor efficacy, and it remains controversial whether IBD-related therapeutics should be continuously used. FMT may be a viable therapeutic approach for IBD combined with CDI. Recently, one study evaluated the feasibility and safety of FMT in 10 children with UC. After FMT by retention enemas (freshly prepared fecal enemas) daily for 5 d, 78% and 67% of patients achieved a clinical response within 1 wk and 1 mo, respectively[108]. Overall, studies of FMT in IBD are rare and restricted to case series or reports, so the available evidence is limited and weak. However, FMT still has the potential to be an effective and safe treatment when standard IBD management has failed. Compared with CD, the efficacy of FMT in UC is more promising, but further investigation is required[33,39,109]. Moreover, except for refractory IBD, it is

Table 2 Main case series and reports of fecal microbiota transplantation in inflammatory bowel disease treatment

Ref.	IBD type (*n*)	Stool material	Volume infusion	Infusion route	Frequency	Donor relationship	Characteristics of outcomes
Bennet *et al*[34], 1989	UC (1)	NR	NR	Enema	1	NR	Documents remission for 6 mo and cease medications
Borody *et al*[144], 1989	UC (1)	NR	NR	Enema	NR	NR	Documented remission for 3 mo and cease medications.
Borody *et al*[35], 2003	UC (6)	Fresh	200-300 g/ 200-300 mL	Enema	6	Related or unrelated	Documented remission from 1 to 13 yr and cease medications
Hamilton *et al*[112], 2012	UC combined with CDI (4)	Fresh or frozen	220-240 mL	Colonoscopy	1	Related or unrelated	Colitis activity was improved, and CDI was cured
Zainah *et al*[145], 2012	UC combined with CDI (1)	Fresh	300 mL	Colonoscopy	1	Related	Documented symptom-free for 8 mo without CDI recurrence
Borody *et al*[146], 2012	UC (3)	Fresh	NR	Repeated rectal infusions	Daily infusion for 2 to 6.5 mo	Related or unrelated	Documented improvement from 1 to 36 mo
Patel *et al*[147], 2013	UC combined with CDI (3)	Fresh	18-397 g/ 180-600 mL	Colonoscopy	1	Related or unrelated	Symptoms such as diarrhea improved or resolved 3 mo after FMT
Angelberger *et al*[105], 2013	UC (5)	Fresh	17-25 g/250 mL + 6-12 g/100 mL	Nasojejunal tube + enema	3	Unrelated	None of cases achieved remission, but only one case was response to FMT by week 12; two cases deteriorated 4 wk after FMT
Kump *et al*[148], 2013	UC (6)	Fresh	300-500 mL	Colonoscopy	1	Unrelated	Documented improvement, but no remission within 2 wk after FMT
De Leon *et al*[110], 2013	UC combined with CDI (1)	Fresh	600 mL	Colonoscopy	1	Related	UC relapse 9 d after FMT
Kunde *et al*[108], 2013	UC (10)	Fresh	165 ml	Enema	5	Related	78% and 67% subjects achieved clinical response within 1 wk and 1 mo after FMT, respectively
Borody *et al*[144], 1989	CD (1)	NR	NR	Enema	NR	NR	Symptoms-free and receiving no medications 4 mo after FMT
Grehan *et al*[118], 2010	CD (1)	Fresh	200-400 mL	Colonoscopy + enema	1 + 9	NR	CD related improvement was not reported
Hamilton *et al*[112], 2012	CD combined with CDI (6)	Fresh or frozen	220-240 mL	Colonoscopy	1 or 2	Related or unrelated	Two cases accepted the second FMT due to CDI recurrence, but the efficacy of FMT on CD was not reported
Patel *et al*[147], 2013	CD combined with CDI (2)	Fresh	18-397 g/ 180-600 mL	Colonoscopy Upper endoscopy	2	Related or unrelated	CDI recurred in 1 case after the first FMT by colonoscopy, and a second FMT was performed by upper endoscopy; but the efficacy of FMT on CD was not reported
Gordon *et al*[109], 2013	CD (1)	Fresh	NR	NR	NR	Related	Response to FMT for 6 mo and then relapsed
Quera *et al*[149], 2013	CD combined with CDI (1)	NR	NR	Colonscopy	NR	NR	Transient bacteremia occurred 24 h after FMT Documented symptom-free 5 mo after FMT and CDI disappeared
Zhang *et al*[36], 2013	CD (1)	Fresh	150 mL	Gastroscope	1	Related	Documented clinical remission for more than 9 mo

FMT: Fecal microbiota transplantation; UC: Ulcerative colitis; CDI: *Clostridium difficile* infection; CD: Crohn' disease; NR: Not reported.

not yet clear whether FMT has any potential therapeutic value for IBD patients induced into remission *via* conventional medical therapy or those with mild IBD.

With regard to adverse events of FMT in IBD treatment, some patients may exhibit belching, abdominal distension, abdominal colic, diarrhea, constipation and other short-term symptoms. Fever and a temporary increase of C-reactive protein can develop transiently after FMT[105]. However, most of these discomforts and symptoms disappear within 2 d after transplantation[37]. Furthermore, other rare complications such as GI bleeding and peritonitis are mainly related to the endoscopic procedures in the process of FMT. Few serious adverse events occur during treatment of IBD by FMT, but it is noteworthy that IBD-related symptoms can be aggravated by FMT in some cases with moderate to severe UC[105]. Furthermore, one case report showed that FMT caused UC-related intestinal inflammation in one elderly male patient with CDI, who had been in long-term remission of UC for > 20 years without any UC-related treatment[110]. Moreover, the long-term follow-up data of FMT such as infection, intestinal inflammation and tumors are still lacking, and need to be further investigated. Nevertheless, there are many impediments limiting the therapeutic potential of FMT in IBD[111], such as rare FMT trials in IBD, ethical and social issues, poor screening of donors, no standard administration of FMT, no standardized preoperative preparation and pretreatment, no standardized preparation of fecal samples, and a lack of FMT-related basic investigations. All the above-mentioned limitations will

Table 3 Donor selection for fecal microbiota transplantation

Absolute exclusion criteria[32,104,124]
Failed to provide informed consent
Systematic and local microbial infections (*e.g.*, pathogenic bacteria, virus, ova and parasites)
Current communicable diseases
Malignancy and chemotherapeutics administration
Chronic gastrointestinal disorders
Peptic ulcer diseases
Gastroesophageal reflux disease
GI polyposis
Inflammatory bowel disease
Irritable bowel syndrome
Chronic constipation
Traveler's diarrhea
Current GI symptoms
Antibiotics administration
Immunosuppressive agents and biological agents
Other medications impact on the gut microbiota (*e.g.*, proton pump inhibitor, prokinetic agents, steroids, aspirin, probiotics, *etc.*)
High-risk lifestyles (*e.g.*, intravenous drug abuse, risk sexual behaviors, *etc.*)
Relative exclusion criteria[32,104,124]
Age < 18 and > 70 yr
History of major GI surgery
Metabolic syndrome
Diabetes mellitus
Abnormal body mass index (< or > 18-25 kg/m^2)
Systemic autoimmune disease
Atopic diseases(*e.g.*, asthma and eczema)
Chronic pain syndromes (*e.g.*, chronic fatigue syndrome and fibromyalgia)
Neuropsychiatric diseases

Table 4 Donor screening for fecal microbiota transplantation

Common and entail serologic screening items[32,124]
Blood routine
Blood biochemistry
Human immunodeficiency virus-1 and -2
Hepatitis A, B and C virus
Syphilis
Helicobacter pylori
Human T lymphotropic virus
Cytomegalovirus
Epstein-barr virus
Common and entail stool screening items[32,124]
Stool routine
Clostridium difficile toxin A/B
Salmonella sp.
Shigella sp.
Campylobacter sp.
Escherichia coli O157
Staphylococcus aureus
Yersinia
Helicobacter pylori
Vibrio parahaemolyticus and *Vibrio cholerae*
Candida albicans
Rotavirus
Cryptosporidium
Giardia
Cyclospora
Isospora
Ova and parasites

be discussed in the following sections.

BARRIERS AND FUTURE DIRECTIONS OF FMT CLINICAL PRACTICE IN IBD

Screening and selecting criteria for donors

Microbiota donation has a higher requirement for the screening of donors in the management of patients undergoing FMT, compared with blood donation. The donor must provide informed consent and detailed medical certificates including medical history, relevant examinations, stool and serological testing. Currently, the donor's inclusion and exclusion criteria are mainly from the self-determined standards of different studies and are more consistent overall, and are listed in Table 3. The feces and serological screening for common and known microbial pathogens are shown in Table 4. The donors are mainly selected from individuals who are closely related to the recipient including intimate partners, family members, and friends, whose microecological environment may be similar to that of the recipient; therefore, a more positive outcome to FMT may be produced, at least theoretically. Most opinions are that the stools from relatives or friends of the recipients show better efficacy compared with those from unrelated donors, and the difference in sex between donor and recipient had little impact on disease remission, but this conclusion is still lacking evidence[99]. Unrelated healthy individuals are also potential donors. Donor feces can be frozen and thawed without loss of effectiveness, enabling FMT-related microbiota banking[112]. In addition, the human intestinal microbiota can be divided into three types: *Bacteroides*, *Prevotella* and *Ruminococcus* by the high-throughput sequencing methods[24]. This means that matching enterotype between donor and recipient based on metagenomic analysis may improve the therapeutic efficacy of FMT. At present, FMT from a healthy donor is mainly used to perform allogeneic FMT. The fecal samples are mainly obtained from a related or unrelated healthy donor, who must face the series of ethical issues in receiving another person's feces, and the effects of the donor's intestinal microbiota on the intestinal immune and pathophysiological functions are unclear without effective theoretical supports. For those patients with mild IBD, it may be good that the fecal samples can be collected and stored in the remission stage and offered to the same patients when they come into the active stage of IBD. However, whether autologous or allogeneic FMT can relieve IBD-related clinical symptoms and induce/maintain the remission of IBD effectively is worthy of further investigation.

Preoperative preparation of donor and recipient

At present, a standardized method of IBD-related preoperative preparation for FMT has not been established[52]. The donor should be administered a gentle osmotic laxative the night before FMT, and should avoid any infections between screening and time of donation. For the FMT recipient, large-volume bowel preparation (*e.g.*, polyethylene glycol) is required regardless of the route of

FMT. In addition, GI motility inhibitors such as loperamide may be optional for the retention of transplanted microbiota, and proton pump inhibitors should be given to recipients before FMT *via* upper GI routes. Importantly, current studies claim that IBD patients who intend to receive FMT need to receive antibiotic pretreatment[35,105], although it still needs to be verified whether antibiotic pretreatment is necessary. In animal models, antibiotic pretreatment before FMT can cause serious damage to the intestinal microbiota structure and may affect the intestinal colonization of the donor's microbiota[113].

Preparation of fecal samples

Generally, the preparation of fecal samples for IBD treatment can refer to the FMT guidelines for treating CDI[32]. FMT practitioners face many challenges in implementing protocols for donor fecal preparation in a clinic setting. Donor fecal samples should be kept in an airtight container and chilled. The samples should be delivered to the institution preferably within 6 h of passage to undergo dilution with proper diluents such as normal saline, homogenization with a blender to achieve a liquid slurry, and filtration to remove particulate matter[39]. Several issues should be noted during the fecal preparation. Initially, the majority of studies utilized fresh fecal material, which means that the fecal collection, preparation and transplantation should be performed on the day of planned FMT[102]. However, fresh fecal material for FMT is not always practical due to issues including delay caused by screening tests, sanitation and aesthetics. Several studies have confirmed that frozen donor fecal material has equal efficacy in the treatment of recurrent CDI compared with fresh fecal material[112]. The frozen material preparation should be processed within 2 h of collection; the specific steps of which are in accord with those of fresh fecal material; the finished fecal suspensions should be stored at -80 ℃ after adding sterile glycerol. On the day of FMT, the frozen material is thawed and diluted with sterile normal saline[112]. Importantly, the frozen preparation is beneficial to establish the FMT-related gut microbiota banks.

In addition, the ideal volume of fecal material for instillation has not been standardized. A systematic review showed that > 500 mL of fecal suspensions allowed 97% of patients with recurrent CDI to achieve remission, while only 80% of patients obtained remission with 200 mL of fecal suspensions[99]. However, it is difficult to standardize the procedure due to the different diluted concentrations of fecal material. Use of < 50 g fecal material may increase the relapse rate of CDI by four times compared with > 50 g fecal material[99]. Overall, practitioners who regularly perform FMT favor 50-60 g of 250-300 mL diluent, respectively[104]. Larger volumes (*e.g.*, 250-500 mL) should be used for delivery from the lower GI tract (*e.g.*, *via* colonoscopy or enema), and smaller volumes (*e.g.*, 25-50 mL) should be used for delivery from the upper GI tract (*e.g.*, *via* a nasoenteric or nasogastric tube). FMT practitioners prefer normal saline, sterile water or 4% milk to dilute the stool sample at present, but which is the optimal diluent still needs to be investigated[99].

Route of FMT administration

FMT is mainly performed *via* the lower GI route, including colonoscopy and retention enema, and/or *via* the upper GI route such as nasoenteric tube, nasogastric tube and gastroduodenoscopy. To date, approximately 75% of cases with recurrent CDI worldwide are administered with FMT *via* the lower GI tract and 25% *via* the upper GI route[104]. FMT *via* the lower GI tract may be more effective than *via* the upper GI tract, although this has yet to be validated[99,100]. Until 1989, retention enema was the most common technique for FMT; however, various alternative methods including nasoenteric tube, gastroscopy and colonoscopy have been used subsequently. A recent long-term follow-up study that involved 77 patients with recurrent CDI showed that colonoscopic FMT was well received by participants and was highly successful, with an overall primary cure rate of 91% and a secondary cure rate of 98%[101]. Moreover, a systematic review showed that colonoscopic FMT had a higher cure rate (91%) for recurrent CDI, compared with the other upper GI routes[99]. Colonoscopic FMT has even been proposed as first-line therapy for the treatment of CDI[114]. For example, the fecal suspensions are sprayed through the biopsy channel of colonoscopy from the terminal ileum, while the colonoscopy is slowly removed until approximately 500 mL of fecal suspensions thoroughly perfuse the colon. Patients should avoid defecation within 1 h after FMT. In patients with severe colitis and significant colonic distention, colonoscopy may be technically challenging and potentially dangerous. Until now, few studies have directly compared routes of FMT administration.

A recent RCT demonstrated that 81% of patients had resolution of recurrent CDI after the first FMT by duodenal infusion[102]; the remarkable cure rate by the nasoenteric tube matched that of colonoscopic FMT. FMT through the upper digestive tract is easy to perform and has a low risk, but it remains unclear whether donor fecal material can be distributed throughout the full colon and increase the risk of small intestinal bacterial overgrowth. According to the optimal FMT route for IBD, a study that involved IBD cases worldwide showed that up to 80% of IBD patients were administered FMT by colonoscopy and/or retention enema[33]. Overall, there are many unanswered questions regarding the best route of administering FMT; the standardized and optimal route for FMT is determined by the needs and status of the patients, and the intestinal microbiota characteristics[103].

Potential therapeutic mechanisms of FMT

Theoretically, the fecal suspension from a healthy donor can reconstruct the damaged intestinal microbiota, restore the intestinal colonization resistance and defend against colonization and infection with *C. difficile* and other pathogenic microorganisms. Thus, the imbalanced structure and function of the intestinal flora is restored

to improve the relevant clinical symptoms. However, the beneficial changes in the intestinal flora generated by FMT and its potential mechanisms are still not clear. Recently, high-throughput sequencing and bioinformatics techniques have been widely applied to describe the intestinal microbial community structure and functions. So far, only a few studies have been conducted that aim to analyze the restoring mechanisms of FMT on the recipient's damaged intestinal microbiota. Several studies based on the bacterial 16S rDNA-based sequencing analysis in recurrent CDI patients found that the diversity and richness of fecal microbiota was clearly reduced[115-117]. The significant changes in *Clostridiales* and *Lactobacillales* from the phylum *Firmicutes*, and *Enterobacteriales* from the phylum *Proteobacteria* could be observed between recurrent CDI and post-FMT patients and healthy donors[116]. The fecal microbiota of recurrent CDI patients becomes more similar to that of healthy donors after FMT, which means that FMT has a permanent action in improving the damaged intestinal microbiota and the clinical symptoms of the recipient[116,117]. Moreover, the reconstructive efficacy of FMT can be maintained for a long time and last for 24 wk[118]. Recently, one study based on the 16S rDNA pyrosequencing showed that abundant donor-related bacterial microbiota could be established in UC recipients, but the efficiency and stability of donor microbiota colonization varied greatly[105]. Several anti-inflammatory and/or short-chain-fatty-acid-producing species such as *F. prausnitzii*, *Rosebura faecis* and *Bacteroides ovatus* were only able could colonize successfully in one UC patient with a positive clinical response after FMT for up to 12 wk[105]. Overall, the influence of FMT on the structure/stability of the intestinal microbiota in IBD patients remains unclear. More longitudinal human and animal studies are needed to verify the permanent reshaping mechanism of FMT. At present, metagenomic analysis combined with germ-free animals, human flora-associated animals, and the chemostat gut models *in vitro* can be used to investigate the mechanism of FMT-related restoring of intestinal microbiota.

An investigational new drug application for FMT

Recently, the US Food and Drug Administration (FDA) has tightened the regulations of FMT, because the complex nature of the fecal microbiota products present specific scientific and regulatory challenges. FDA has announced that fecal microbiota collected from healthy individuals is a biologic product, meaning physicians must submit an investigational new drug (IND) application. However, published data have confirmed the astounding efficacy of FMT, which may be the best therapeutic modality for the treatment of recurrent CDI.

Physicians and scientists are concerned that it is no easy task to file the IND application for FMT practitioners, which could make FMT unavailable and suggest an alternative regulatory approach to ensure the widespread availability of FMT for those patients with recurrent CDI. FDA has acknowledged these concerns and has published the alternative enforcement discretion regarding the IND requirements for the use of FMT to treat CDI not responding to standard therapies. FDA intends to exercise this discretion provided that the FMT practitioners obtain adequate informed consent for the use of FMT products, stating that FMT products to treat CDI are investigational drugs, and explaining any potential risks for FMT treatment. Unfortunately, the use and study of FMT for diseases or conditions other than CDI is not included in this enforcement discretion policy. Therefore, physicians wishing to ensure access to FMT for IBD or other conditions need to file an IND application. Recently, several articles provided step-by-step guidance to physicians on how to navigate the regulatory requirements of FDA and prepare the IND application for FMT[40,119]. The use of an IND will also allow collection of more data on the efficacy and safety of FMT and likely further support its use. Except for the application of IND, the clinical application of FMT in IBD still faces many issues. Once these issues are addressed, standardized clinical trials can move forward with the hope of not only increasing access to FMT but also developing a well-tolerated and reliable drug that decreases any potential long-term consequences from FMT.

Patients' attitudes toward FMT

Patients are a powerful evolutionary force, whose perceptions and attitudes are important for the clinical application of FMT. A survey showed that up to 95% of adult UC patients and parents of children with UC would consider FMT and are eager for it to become available[120,121]. Moreover, a long-term follow-up study among patients who had FMT for recurrent CDI showed that 97% of patients were willing to receive another FMT once CDI occurred in the future, and 53% of patients claimed to choose FMT as the first treatment option for substitution of antibiotics[101]. Another survey reported that when aware of the fecal nature of FMT, 81% of patients still consider it as an alternative treatment for recurrent CDI, especially when recommended by physicians[122]. Patients recognize the inherently unappealing nature of FMT, but they are nonetheless open to considering it as an alternative treatment for recurrent CDI. Overall, the strong willingness of patients has important implications for the clinical application of FMT and the other microbiota-based treatments in the future.

Synthetic microbiota transplantation

Emerging data showed that two recurrent CDI patients were cured by synthetic microbiota transplantation (SMT) instead of FMT; the synthetic stool was composed of 33 bacterial strains isolated from the feces of an unrelated donor, grown in culture and subsequently administered as a suspension in sterile normal saline[123]. SMT composed of large numbers of well-defined bacterial strains derived from stools, combined with FMT, can be defined as microbial ecosystem therapeutics[124]. Recently, the concept of "Robogut" has been proposed[28], which is actually

a type of chemostat. The chemostat *in vitro* mimics the human gut, even the whole GI tract, and is mainly composed of complex media, a pH and temperature monitor, anaerobic gas, and a stirrer[28].

For several decades, microbial ecologists have been trying to develop a chemostat resembling the human gut, in which a probiotic gut microenvironment consisting of beneficial anaerobic microbial species by the continuous culture can be manufactured[125]. SMT based on the chemostat resembling the human gut can be viewed as the next logical step in the development of microbiota therapeutics. For example, if the beneficial bacterial species could be cultured artificially and combined into flora with optimal proportion and magnitude to achieve standardized SMT, the safety and controllability of bacterial origin can be ensured, thus enabling effective quality control and reducing the process of screening donor. Moreover, the synthetic bacteria can be made of freeze-dried powder or capsules in the future to restore the disturbed intestinal microbiota, thereby curing those conditions associated with gut dysbiosis.

CONCLUSION

Evidence from animal and human studies strongly supports the role of intestinal microbiota in the etiology of IBD. The single microbial pathogen in IBD is still undefined, which may not contribute to the onset of IBD. However, many studies based on culture-independent techniques have confirmed aberrant intestinal microbiota and its metabolites in patients with IBD, although whether the intestinal microbiota is the initiating factor in IBD or is secondary to IBD is still not resolved. The present single or combined probiotic products have modest efficacy in IBD treatment; most of which are supplementary therapeutics. FMT is the most radical way to restore the disturbed homeostasis of intestinal microbiota in IBD, but there has been no consensus regarding the selection and screening of donors, the optimal volume and route of administration, pretreatment and preparation before transplantation, efficacy durability and long-term safety profiles. In addition, studies on the mechanisms of FMT for the recovery of intestinal microbial homeostasis and host immunity are still lacking, thus not providing adequate theoretical support for clinical application of FMT.

Currently, FMT application is mainly driven by its remarkable efficacy and the strong demand of clinicians and patients, while institutions have not paid much attention to FMT, especially in technological innovation for the preparation of fecal microbiota products. Moreover, many case series have shown the clinical efficacy of FMT in the management of refractory IBD; several controlled clinical trials have been registered (www.clinicaltrials.gov) and are underway to evaluate the efficacy of FMT in IBD. The hypothesis that whether autologous or allogeneic FMT can induce and maintain persistent remission of mild IBD needs to be confirmed by animal models and pilot clinical trials. At present, data related to the use and study of FMT to treat IBD other than CDI are still limited. Compared with FMT in CDI treatment, FMT in the management of IBD has to face more rigorous IND application. In addition, SMT as a promising microbiota therapeutic option should also be evaluated rigorously by germ-free and human flora-associated animal models, and the chemostat gut model *in vitro* may also be an excellent technique for the evaluation and production of SMT. Microbiota pathogenesis and therapeutics in IBD is a promising field, and identification and resolution of key issues are imperative to move this field forward.

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