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Relationship between intestinal microbiota and ulcerative colitis: Mechanisms and clinical application of probiotics and fecal microbiota transplantation

Zhao-Hua Shen, Chang-Xin Zhu, Yong-Sheng Quan, Zhen-Yu Yang, Shuai Wu, Wei-Wei Luo, Bei Tan, Xiao-Yan Wang

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Abstract

Ulcerative colitis (UC) is an inflammatory disease that mainly affects the colon and rectum. It is believed that genetic factors, host immune system disorders, intestinal microbiota dysbiosis, and environmental factors contribute to the pathogenesis of UC. However, studies on the role of intestinal microbiota in the pathogenesis of UC have been inconclusive. Studies have shown that probiotics improve intestinal mucosa barrier function and immune system function and promote secretion of anti-inflammatory factors, thereby inhibiting the growth of harmful bacteria in the intestine. Fecal microbiota transplantation (FMT) can reduce bowel permeability and thus the severity of disease by increasing the production of short-chain fatty acids, especially butyrate, which help maintain the integrity of the epithelial barrier. FMT can also restore immune dysbiosis by inhibiting Th1 differentiation, activity of T cells, leukocyte adhesion, and production of inflammatory factors. Probiotics and FMT are being increasingly used to treat UC, but their use is controversial because of uncertain efficacy. Here, we briefly review the role of intestinal microbiota in the

pathogenesis and treatment of UC.

Key words: Fecal microbiota transplantation; Intestinal microbiota; Ulcerative colitis; Probiotics; Mechanism; Clinical application

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Core tip: As we all know, genetic factors, host immune system disorders, intestinal microbiota dysbiosis, and environmental factors contribute to the pathogenesis of ulcerative colitis (UC). In this review, we explore the mechanism and clinical application of intestinal microbiota such as probiotics and fecal microbiota transplantation in UC so that we can use these tools to cure more diseases. Enteric microbiota leads to new therapeutic strategies for UC.

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INTRODUCTION

The etiology and pathogenesis of ulcerative colitis (UC) are complex. UC is believed to be caused by an imbalance between intestinal microbiota and mucosal immunity, resulting in excessive intestinal inflammation^[1]. Thus, dysbiosis of intestinal microbiota contributes to the pathogenesis of UC. In UC patients, the intestinal microbial population and functional diversity and stability of intestinal bacteria are impaired, with reductions in specific Firmicutes bacteria and increased Bacteroidetes bacteria and facultative anaerobes^[2].

Probiotics are increasingly being used to treat UC. Probiotics are living nonpathogenic bacteria, such as *Lactobacillus*, *Bifidobacterium*, and *Enterococcus*^[3]. The bacteria in probiotics can benefit the intestinal and immune systems^[4]. Probiotics can restore the function of disturbed mucosal barrier^[5], correct intestinal microbiota imbalance, inhibit competition of potential pathogens, improve local and systemic immunity, and enhance intestinal barrier function^[6]. Probiotics can effectively induce and maintain remission in UC patients, suggesting that optimizing intestinal microbiota is key in the treatment of UC.

Fecal microbiota transplantation (FMT) also shows promise in UC. FMT aims to quickly restore the normal function and composition of intestinal microbiota, which can help treat intestinal and parenteral diseases. How FMT improves inflammatory bowel disease (IBD) is not completely understood. Studies have shown

that after FMT, the intestinal microbiota composition of recipients was consistent with that of the donors^[7]. The mechanisms of action of FMT might be the competitive inhibition of pathogenic microorganisms and improvement of immunity and metabolism.

PATHOGENESIS OF UC

The pathogenesis of UC is complex and it is believed to be mediated by genetic susceptibility, microbial dysregulation, and environmental factors. In UC, mucosal permeability increases and the inflammatory reaction is caused by excessive reaction below the lymphoid tissue^[8]. There exists impaired ileum barrier function, the reduction of mucin and goblet cells which produce mucin, and the decrease of epithelial NLRP6 in UC patients^[9].

INTESTINAL MICROBIOTA

The intestinal microbiota and the bacteria that compose it, such as Firmicutes, Bacteroidetes, and Actinomycetes, are still not well understood^[10,11]. According to aerobiosis or anaerobiosis, the intestinal microorganisms are divided into anaerobic bacteria, facultative anaerobic bacteria, and aerobic bacteria; anaerobic bacteria are the most abundant intestinal bacteria^[12]. These bacteria are mainly distributed in the colon and distal small intestine. Most of the bacteria live on the surface of the intestinal mucosa. They attach to the surface of the intestinal epithelial cells to form a layer of bacterial biofilm, which ultimately affects the intestinal metabolism of nutrients, intestinal permeability, and intestinal immune system function.

According to their role in the host, intestinal microbiota can be divided into three categories. The first category contains the physiologic bacteria that are symbiotic with the host. They attach to the deep mucosal epithelial cells, and most are anaerobic bacteria. They are the dominant microbiota of the intestine (*e.g.*, *Bifidobacterium*, *Bacteroides*, and *Peptococcus*) and play key roles in nutrition and immune regulation. The second category contains conditional pathogens that inhabit the host. They are mainly facultative aerobic bacteria and intestinal nondominant bacteria (*e.g.*, *Enterococcus* and *Enterobacter*). These organisms are harmless when intestinal microecological balance is maintained but can be harmful to humans under certain conditions. The third category contains mostly pathogens (*e.g.*, *Proteus* and *Pseudomonas*). When microecology is in balance, long-term colonization of pathogens is rare, and the number of these organisms is small and nonpathogenic. If changes in the enteral and external environments lead to a decline of intestinal-dominant microbiota, then intestinal microbiota imbalance will occur, with pathogens or conditional pathogens increasing to the point of causing disease.

Intestinal mucosal symbiotic bacteria promote intestinal stability. Symbiotic bacteria help inhibit intestinal colonization by pathogens. Highly evolved bacteria occupy the intestine and prevent pathogens from invading the lamina propria layer. Intestinal bacteria stimulate the intestinal mucosa by causing a low level of inflammation. This inflammation contributes to the formation and improvement of the intestinal immune system, which monitors and removes harmful bacteria to maintain the body health. Intestinal bacteria also participate in important physiologic metabolic activities. *Propionibacterium freudenreichii ET-3* can produce large amounts of vitamin K₂ precursor material, which can activate aroma receptors, participate in substance metabolism, and detoxify and inhibit dextran sodium sulfate-induced colitis *in vivo*^[13]. When the composition of intestinal symbiotic bacteria changes, the intestinal microbiota becomes unbalanced, causing an intestinal immune response^[14].

Microorganisms release many biologically active substances, such as intestinal short-chain fatty acids (SCFAs), which have a strong immunomodulatory effect. Acetic acid, butyric acid, and propionic acid are the most abundant SCFAs^[15]. SCFAs act as the main energy substrates and directly influence the host digestive tract through phenotypic alteration of colonic epithelial cells. They can also act as tumor suppressors and have recently been shown to be modulators of the intestinal neuroendocrine system. In addition, SCFAs are involved in anti-inflammatory gene regulation processes both *in vitro* and *in vivo*^[16]. *Faecalibacterium (F.) prausnitzii* and *Roseburia* are butyric acid-producing bacteria that are usually considered as probiotic microorganisms. Butyrate can protect the integrity of the intestinal epithelium, promote the intestinal immune response, inhibit the growth of tumor cells, and reduce the activity of cancer-promoting enzymes, thus protecting the intestinal wall and reducing intestinal inflammation and colorectal cancer incidence^[17].

INTESTINAL MICROBIOTA AND UC

There is close relationship between the pathogenesis of UC and intestinal microbiota. The steady state of the intestinal microbiota is important in preventing the excessive growth of certain microorganisms. Dysbiosis of the intestinal microbiota may be a contributing factor in some diseases and conditions, such as obesity, metabolic syndrome, autoimmune diseases, necrotizing enterocolitis, skin disease, UC, Crohn's disease (CD), and irritable bowel syndrome^[18]. When the balance of intestinal microbiota is broken, the intestinal defense function and immunoregulatory function are decreased, the immunity of the body is reduced, and the relative pathogenic factors are increased so as to cause the intestinal mucosal invasion or aggravate the diseases.

The pathogenesis of UC is complex, and the interaction between the host and intestinal microbiota may be a key factor. Under normal circumstances, the host's innate and adaptive immunity prevents the invasion of harmful bacteria while tolerating the normal microbiota. However, if the microbiota is imbalanced, immunity is compromised. The intestinal mucosal immune response is overstimulated, which can lead to disease^[19].

Disrupted intestinal microbiota can cause intestinal inflammatory responses. Disruption in the microbiota results in a rapid increase in harmful bacteria in the intestine. In addition, release of enterotoxin increases intestinal mucosal permeability, and production of immunosuppressive protein results in immune dysfunction. Growing populations of harmful bacteria directly invade and damage the intestinal epithelial cells, resulting in damage to the intestinal mucosal barrier. Excessive growth of some bacteria affects metabolic and energy metabolism, triggering intestinal inflammation and damage of the intestinal mucosa. Intestinal mucosal barrier function declines, the shield function of the intestinal wall diminishes, and intestinal microbiota is translocated, which further damages the intestinal mucosal barrier, causing a vicious cycle and aggravating the intestinal inflammatory response. Animal experiments have found that colitis can be induced in animal models by disrupting intestinal bacteria. Sterile animals with IL-10 or HLA-B27 knockout did not develop colitis^[20], suggesting that intestinal microbiota is essential for the occurrence of UC.

A large number of bacteria are adhered to intestinal epithelial cells of CD patients compared with healthy people. Microbiota might be one of the key factors of activating the intestinal immune system and inducing CD. In addition, the dysregulation of resident microbiota may be the major factor of inducing IBD. The occurrence of intestinal inflammation might cause the production of a variety of different types of instant cell factors.

Microbial pathogens related to UC

Many studies have demonstrated that the composition and function of intestinal microbiota in UC patients are compromised. Some bacteria such as *Akkermansia (A.) muciniphila* are decreased. *A. muciniphila* is one of the most abundant members of the human gut microbiota, representing between 1% and 5% of human intestinal microbes. Several studies have shown a relationship between UC and *A. muciniphila*. *A. muciniphila* was decreased in UC patients, along with *Roseburia* bacteria^[21]. It was also decreased in a mouse model of carrageenan-induced colitis^[22]. Therefore, *A. muciniphila* might be a new target of UC. Abnormal microbiota reduced the complexity of the intestinal microbial ecosystem, which is a common feature of patients with UC and CD^[23]. Several microbial pathogens are possibly related to intestinal inflammation and thus UC patients

may harbor *Mycobacterium avium paratuberculosis*^[24,25], adherent-invasive *Escherichia coli*^[26], *Clostridium (C.) difficile*^[27-29], *Helicobacter* species^[30-32], *Salmonella* species^[33], *Yersinia* species^[34], *Fusobacterium* species^[35], norovirus^[36], and *Listeria* species^[37]. However, the exact pathogenesis is unclear.

SCFA production

In one study, qualitative and quantitative changes were demonstrated in the composition of enteric bacteria in patients with UC^[38]. The diversity of bacteria in UC patients was less than that of the control group. The number of dominant bacteria was decreased, the number of pathogens was increased, and the proportions of each strain of the dominant microbiota were not balanced. Studies have found that the diversity of intestinal microbiota in UC patients is decreased by approximately 25% compared with that of healthy controls. *Firmicutes* and *Bacteroidetes* were decreased, while *Proteobacteria* and *Actinomycetes* were increased. Machiels *et al.*^[39] found that two important butyrate-producing *Firmicutes* bacteria, *Roseburia hominis* and *F. prausnitzii*, were significantly decreased in UC patients. Varela *et al.*^[40] found that the number of *F. prausnitzii* was significantly increased in the remission period of UC, indicating that *F. prausnitzii* may play a vital role in the treatment of UC.

T-cell response

Some bacteria affect the differentiation of T-cell subsets and thus influence the occurrence and development of inflammation. *Bacteroides (B.) fragilis* and capsular lipopolysaccharide A improved the balance of Th1/Th2 cells in mice by activating NF- κ B *via* TLR2 and regulating the secretion of TNF- α and IL-12^[41]. Other studies have found that *B. fragilis* affected the steady state of mucosal T cells by inducing the production of regulatory T (Treg) cells in a 2,4,6-trinitrobenzene sulfonic acid-induced colitis mouse model^[42]. In the small intestine and colon, segmented filamentous bacteria (SFB) can increase the number of Treg cells^[43] and can also regulate the differentiation of Th17 cells and promote the production of IL-22-producing CD4+ T cells. The mechanism might be that SFB stimulates the production of serum amyloid A (SAA), which is an early inflammatory marker, and SAA induces a specific Th17 response *in vivo*^[44]. These findings suggest that lipopolysaccharide A may play a dual role in intestinal homeostasis. Mice treated with *Lactobacillus reuteri* had a higher percentage of Treg cells^[45]. *Clostridium* clusters IV, XIVa, and XVIII secrete SCFAs to stimulate the production of TGF- β by intestinal epithelial cells and induce Treg cell differentiation to promote intestinal mucosal immune tolerance^[46]. Hsp65-producing *Lactococcus lactis* inhibited experimental autoimmune encephalomyelitis, and the mechanism might be related to the induction of CD4+/Foxp3+ and CD4+/

LAP+ Treg cells and the TLR2 signaling pathway *in vivo*^[47] (Figure 1).

MECHANISM AND CLINICAL USE OF PROBIOTICS

Probiotics can promote the secretion of anti-inflammatory factors by improving intestinal mucosal barrier and immune system function and thus inhibiting the growth of harmful bacteria in the intestine. Pathogens can weaken the barrier function of the intestinal mucosa and pass through or damage the mucosal wall. Probiotics can prevent or repair such damage.

The main mechanisms of probiotics include competing for adhesion sites and nutrients, maintaining the balance of normal intestinal microbiota, enhancing intestinal mucosal barrier function, promoting immune tolerance of the intestinal mucosa, interfering with intestinal inflammatory response, and inhibiting intestinal epithelial cell apoptosis. Studies have indicated that probiotics might be useful in the treatment of UC. Through the PI3K/Akt and NF- κ B signaling pathway, probiotics decreased proinflammatory cytokines such as TNF- α and IL-1 β and increased anti-inflammatory factor IL-10, thus improving the symptoms of UC.

Bifidobacterium is one of the first colonizers of the baby intestine and the main microbial organism of the adult intestine^[48]. It is beneficial microbiota that promotes antitumor immunity and prevents recurrence of UC. *Bifidobacterium breve* reduces the shedding of apoptotic epithelial cells in an extracellular polysaccharides- and MyD88-dependent manner^[49].

A meta-analysis containing a total of 1763 cases in 32 clinical trials showed that probiotics significantly increased the clinical remission rate of patients with active UC ($P = 0.01$; risk ratio = 1.51). Probiotics and aminosalicic acid had similar clinical effects. Subgroup analysis showed that VSL#3 (Alfasigma) resulted in the most significant improvement in UC, followed by lactic acid bacteria and *E coli*^[50]. Another study on UC patients aged 12 to 16 years showed that the recurrence rate was lower in the group treated with probiotics for 1 year than in the control group (21% vs 73%)^[51]. One study showed that the addition of *Lactobacillus* species to the usual therapies reduced relapse in UC patients^[52]. Oliva *et al.*^[53] also found that local administration of *L. reuteri* ATCC 5573 with a standard dose of mesalazine reduced inflammation of the rectal mucosa in children with UC. In addition, *E. coli* strain Nissle promoted long-term maintenance of remission in UC patients. Administration of *Saccharomyces boulardii* during treatment with mesalazine induced clinical remission in 71% of patients with active mild to moderate UC^[54,55]. In 2013, Varela and colleagues^[40] investigated the fecal bacteria of 116 UC patients in remission and 16 healthy subjects and found that *F. prausnitzii* colonization was

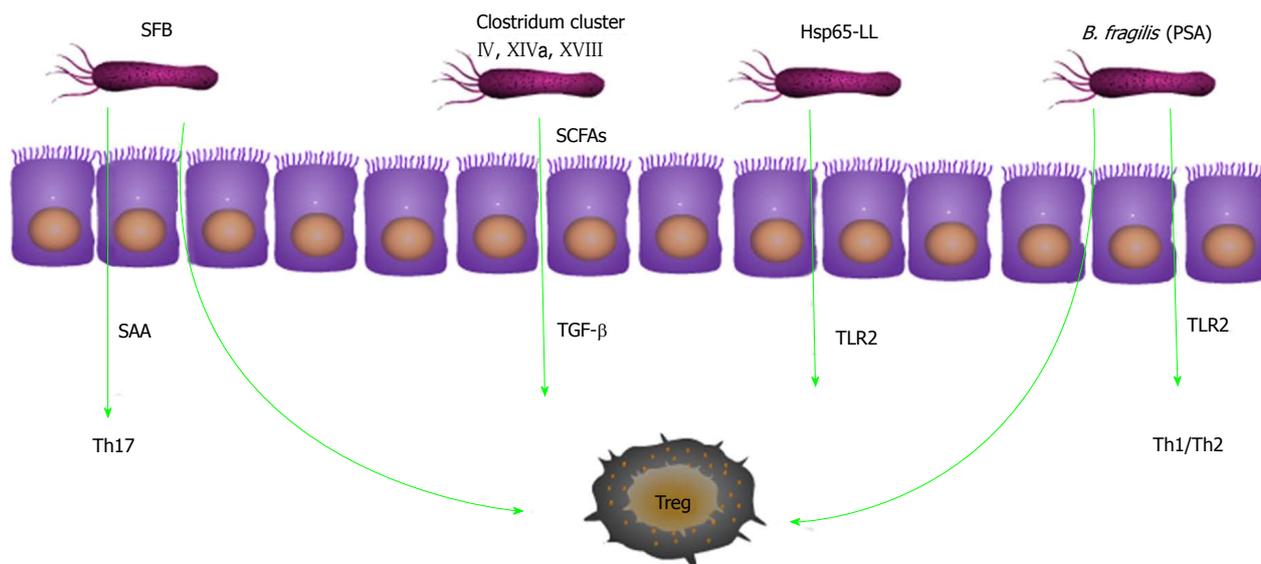


Figure 1 Bacteria affect the differentiation of T-cell subsets and thus influence the occurrence of inflammation. Different types of bacteria have different effects on T cell differentiation. SFB has an effect on TH17. *Clostridium* clusters IV, XIVa, and XVIII and Hsp65-LL can influence the differentiation of Treg cells. *B. fragilis* might affect the ratio of Th1/Th2 via TLR2. SFB: Segmented filamentous bacteria; Hsp65-LL: Hsp65-producing *Lactococcus lactis*; *B. fragilis*: *Bacteroides fragilis*.

significantly reduced in UC patients. In addition, oral administration of *F. prausnitzii* was found to help induce remission in UC patients^[56].

However, the results with probiotics in UC have not been consistent. Studies have shown that probiotics can increase gastrointestinal peristalsis, induce diarrhea in IBD patients, change stool frequency, and increase disease activity^[57]. A study by Wildt *et al.*^[58] demonstrated that there was no difference in UC remission between patients administered with *Lactobacillus acidophilus* LA-5 and *Bifidobacterium* and the control group. Larger sample sizes and more randomized controlled clinical trials are needed to clarify the role of probiotics in the treatment of UC.

MECHANISM AND CLINICAL USE OF FMT

Along with probiotics, FMT is also being investigated as a treatment for UC. FMT is the process of transplanting fecal bacteria from a donor into a recipient. Currently, no standard criteria exist for FMT donor screening^[59]. Donors are often selected from relatives, spouses, friends, or healthy volunteers. The collection of feces is usually conducted on the day of transplantation. The feces are dissolved in saline or water, homogenized, and filtered to form a homogeneous solution. Stools are usually transplanted in 6 to 8 h^[60]. Stool banks exist in many countries and may serve many clinical functions in the future^[61,62]; however, internationally standardized stool banks have not yet been established.

The essence of FMT is to reconstruct intestinal microbiota and cure disease by normalizing abnormal immune and inflammatory responses, the numbers and activities of neurotransmitters and vasoactive

substances, and energy metabolism. FMT is used to treat chronic gastrointestinal infections and IBD^[60]. FMT can improve intestinal microecology and the permeability of the intestinal mucosa. It can activate the intestinal humoral immune response to induce synthesis of IgA, IgG, and IgM through the TLR pathway, thus protecting the intestinal mucosa. FMT can also reduce the pH value of the intestine and increase the adhesion of bacteria and H₂O₂ to competitively inhibit the adhesion and translocation of pathogens^[63]. Finally, FMT can treat immune disorders by inhibiting the secretion of proinflammatory cytokines and promoting Th1 differentiation, T-cell activity, leukocyte adhesion, and immune-stimulatory factors.

In gastrointestinal homeostasis, the diversity of the microbiota prevents colonization and overgrowth of pathogens. FMT can reduce intestinal permeability by increasing the production of SCFAs, thereby reducing the severity of disease. Increased SCFAs, especially butyrate, which is the main source of energy in colonic epithelial cells, maintain the integrity of the epithelial barrier by reducing intestinal permeability. FMT can also restore the dysbiosis of microbiota. The proportions of beneficial bacteria are increased and the diversity is also increased. FMT can make the composition of microbiota be more likely to be similar to the donor for a long time. Recently, a study by Dutta *et al.*^[64] found that FMT increased the diversity of fecal microbiota and increased the proportion of Lachnospiraceae, which are butyrate-producing bacteria. These findings not only confirm the speculated mechanism of action of FMT, but also indicate that Lachnospiraceae might be the key bacteria in the success of FMT. This finding could lead to targeted and standardized FMT.

FMT is successful in treating recurrent *C. difficile*

Table 1 Main case series and reports of fecal microbiota transplantation in ulcerative colitis patients

Ref.	UC (n)	Stool material	Volume infusion	Infusion route	Frequency	Donor relationship	Characteristics of outcomes
Kump <i>et al</i> ^[92] , 2013	15	Fresh	100 to 150 g 300-500 mL	Rectosigmoidoscopy	1	Unrelated	None of the patients achieved CR
Kunde <i>et al</i> ^[75] , 2013	10	Fresh	70 to 130 g 60 mL	Enemas	5	Related	33% patients achieved CR at 1 wk
Angelberger <i>et al</i> ^[72] , 2013	5	Fresh	60 g 250 mL	Nasojejunal tube	5	Related or unrelated	(0/5) patients demonstrated a remission
Suskind <i>et al</i> ^[93] , 2015	4	NR	30 g 100 mL	Nasogastric Tube	1	Related or unrelated	(0/4) patients demonstrated a remission
Kellermayer <i>et al</i> ^[86] , 2015	3	Frozen	NR	Colonoscopy	22-30	A single donor	(3/3) patients demonstrated a remission
Damman <i>et al</i> ^[94] , 2015	7	Fresh	175-290 mL	Colonoscopy	1	Related or unrelated	(1/7) patients demonstrated a temporary remission
Wei <i>et al</i> ^[67] , 2015	11	Fresh	60 g 300 mL	Colonoscopy	5	Unrelated	The Mayo scores of all patients decreased at 4 wk
Cui <i>et al</i> ^[66] , 2015	15	NR	NR	Gastroscope channel	1	1 (73.3%) related; 2 (26.7%) unrelated	28.6% patients achieved CR
Vermeire <i>et al</i> ^[95] , 2016	8	Fresh	100 g 200 mL	Nasojejunal tube or colonoscopy	2	Related	(2/8) demonstrated a remission at week 8

UC: Ulcerative colitis.

Table 2 Recent randomized, controlled trials of fecal microbiota transplantation in ulcerative colitis patients

Ref.	Rossen <i>et al</i> ^[69] , 2015	Moayyedi <i>et al</i> ^[70] , 2015	Paramsothy <i>et al</i> ^[96] , 2017
n (UC/placebo)	48 (23/25)	75 (38/37)	85 (42/43)
UC arm	50 mL, nasoduodenal, healthy donors	50 mL enema, healthy donors	150 mL, colonoscopic, unrelated donors
Placebo arm	Autologous FMT	50 mL enema, water	150 mL, colonoscopic, isotonic saline
Frequency	At weeks 0 and 3	Once weekly for 6 wk	5 d per week for 8 wk
Evaluation criterion	Remission (SCCAI $\leq 2 + \geq 1$ -point decrease in the Mayo endoscopic score) at week 12	Remission (a Mayo score ≤ 2 with an endoscopic Mayo score of 0) at week 7	Remission (Mayo score ≤ 2 , all subscores ≤ 1 , and ≥ 1 point reduction in endoscopic subscore) at week 8.
Results	30% with FMT vs 20% controls ($P = 0.51$)	24% with FMT vs 5% placebo ($P = 0.03$)	27% with FMT vs 8% placebo ($P = 0.021$)

FMT: Fecal microbiota transplantation; UC: Ulcerative colitis.

infection. FMT could also potentially be used to treat UC, although limited evidence exists. Only a few small case series have been reported, and the efficacy is inconsistent, ranging from 20% to 92% (Table 1). There are currently only three randomized controlled trials of FMT in UC (Table 2). Clinical trials have shown differences in efficacy of FMT, which might be due to differences in individual factors, severity of disease, sites of disease, FMT donors, infusion paths, infusion doses, and so on. A recently reported meta-analysis^[65] included 11 studies (containing two randomized controlled trials, one open case-control study, and eight cohort studies) and 133 patients with UC. The results showed that the clinical remission rate was 30.4% in UC patients treated with FMT. There were no significant differences in the remission rates between single and multiple transplantations and between upper digestive tract and lower digestive tract transplantations. In contrast, some reports have indicated that repeated FMT may be better than single transplantation^[66]. Although the remission rate of UC was not ideal, patients' quality of life improved^[67], and FMT is easy to perform and safe. Another meta-analysis of FMT showed that the clinical response rate of IBD was 22%^[68]. After FMT, the intestinal microbiota

diversity of UC patients increased, and the microbiota species converged with those of the donors^[69-71]. However, in time, intestinal bacteria will revert back to the pretreatment state. Therefore, repeated FMT may be needed; thus, the ideal number of treatments and interval between transplantations need to be explored^[72].

ADVERSE REACTIONS OF INTESTINAL MICROBIOTA

Few adverse reactions have been reported with probiotics^[73,74], and FMT has also been regarded as a safe treatment strategy. Adverse events or serious complications of FMT are rarely reported but include abdominal cramps, bloating, constipation, and diarrhea. Fever and increased C-reactive protein level are common, but both are transient and self-limiting^[75]. Other rare adverse reactions include sore throat and headache^[76], abnormally low blood pressure^[77], shingles^[78], the occurrence of UC^[79], norovirus infection^[76], weight gain^[80], peritonitis or enteritis^[81,82], perforation of the colon, pneumonia^[83], and cytomegalovirus infection^[84]. Bacteremia has been reported after FMT^[85]. After FMT, changes in the composition of intestinal microbiota

may lead to changes in gene expression of the mucosal cells of the recipients^[86], alteration of intestinal mucosal immune function^[87], changes in the intestinal ecological environment^[88], and differences in body metabolism^[89]. FMT can affect gastrointestinal diseases as well as extra-gastrointestinal disorders^[90]. Therefore, patients who undergo FMT require long-term follow-up to observe pathologic and physiologic effects of treatment.

In addition, because of the diversity and uncertainty of intestinal microbiota, the current treatment criteria for FMT are difficult to formulate. Controversy concerns whether intestinal microbiota should be managed as a drug or as a bodily organ. These problems hamper the standardization and specific application of FMT. Determining the effective bacteria and the ideal treatment subjects will help to standardize FMT and make treatment more consistent^[91].

CONCLUSION

The pathogenesis of UC is closely related to intestinal microbiota, although the exact bacteria that contribute to UC have not been determined. The use of probiotics in UC is currently being investigated. Probiotics may help normalize the imbalance of intestinal microbiota, improve the microecological environment, enhance intestinal mucosal barrier function, and reduce gastrointestinal infections. However, determination of the specific mechanism and types of probiotics, the best concentrations, and ideal treatment methods requires further study. The treatment of UC with FMT is also promising, but many questions remain regarding this treatment as well. Clearly, more research is needed regarding the use of probiotics and FMT in UC.

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