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Review Article

Microbial Modulation in Inflammatory Bowel Diseases

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
5-ASA, 5-aminosalicylic acid; AE, adverse event; AIEC, adherent-invasive Escherichia coli; BTV, bifid triple viable; CD, Crohn's disease; CDAD, Clostridioides difficile-associated diarrhea; CDI, Clostridioides difficile infection; CFU, colony-forming unit; CI, confidence interval; CRP, C-reactive

ABSTRACT

Gut dysbiosis is one of prominent features in inflammatory bowel diseases (IBDs) which are of an unknown etiology. Although the cause-and-effect relationship between IBD and gut dysbiosis remains to be elucidated, one area of research has focused on the management of IBD by modulating and correcting gut dysbiosis. The use of antibiotics, probiotics either with or without prebiotics, and fecal microbiota transplantation from healthy donors are representative methods for modulating the intestinal microbiota ecosystem. The gut microbiota is not a simple assembly of bacteria, fungi, and viruses, but a complex organ-like community system composed of numerous kinds of microorganisms. Thus, studies on specific changes in the gut microbiota depending on which treatment option is applied are very limited. Here, we review previous studies on microbial modulation as a therapeutic option for IBD and its significance in the pathogenesis of IBD.

Keywords: Inflammatory bowel diseases; Microbiota; Dysbiosis; Probiotics; Antibiotics; Fecal microbiota transplantation

INTRODUCTION

The prevalence of inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD), has been increasing worldwide, particularly in Asian countries (1-3). The increase in prevalence has resulted in an increase in the morbidity of because of the characteristics of the disease, including disease onset at a young age and the life-long course of the disease, which includes multiple relapses and remissions (1). Although IBD is a multifactorial disease, recent studies have found that microbial dysfunction is one of the principal factors in its pathogenesis (4-6). Microbial imbalances and intestinal mucosal barrier dysfunction can cause immune intolerance, which is a primary feature of the initial stages of IBD (4). However, their detailed relationships (cause and effect; incidental or consistent; role of invasive organisms such as bacteria, viruses, and fungi; and genetic susceptibility) remain to be elucidated. The Human Microbiome Project and the development of molecular techniques such as next-generation sequencing (NGS) have allowed specific and detailed research on the microbiome and its association with human diseases. The gut microbiota is an assembly of microorganisms that engraft into the human intestine during and after birth. After birth, the microbiota is influenced by various factors (7,8). Recently,

protein; DSS, dextran sulfate sodium; ESR, erythrocyte sedimentation rate; FMT, fecal microbiota transplantation; GPR, G-protein coupled receptors; hCRP, hypersensitive CRP; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IPAA, ileo-anal pouch anastomosis; MAP, Mycobacterium avium subspecies paratuberculosis; NGS, next-generation sequencing; NLR, nucleotide-binding oligomerization domain-like receptors; NOD, nucleotide-binding oligomerization domain-containing protein; PRR, pattern recognition receptor; RCT, multicenter randomized controlled trial; RR, relative risk; UC, ulcerative colitis.

Author Contributions

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there has been numerous of research on gut dysbiosis and its association with various diseases, including IBD (6,9,10). Modulation of the intestinal microbiota to correct dysbiosis has been investigated as a treatment option for IBD. Here, we review the role of dysbiosis in the pathogenesis of IBD and the use of antibiotics, probiotics, synbiotics, or fecal microbiota transplantation (FMT) for microbial modulation as treatment options for IBD.

PATHOGENESIS OF IBD

Although the pathogenesis of IBD remains to be elucidated, recent advances in molecular biology and immunology have provided a more detailed etiology for this disease (**Fig. 1**) (4). Briefly, intestinal inflammation results from an imbalance between the intestinal epithelium, mucus layer, microbiota, and immune cells in the intestine (4). Genome-wide association studies have revealed more than 240 risk variants related to IBD pathogenesis, including genes involved in intracellular signaling, epithelial barrier maintenance, and innate or adaptive immunity pathways (11). Searching for and analyzing risk variants in patients with IBD might provide clues to identify the genes and biological pathways involved in IBD and their roles in IBD development (4).

Dysbiosis (distinctive microbial changes) in IBD

Gut dysbiosis can be defined as a state in which there is a decrease in the levels of protective bacteria along with an increase in the levels of pathogenic bacteria in the intestine (12). Considering that the term "dysbiosis" is a relatively vague expression, efforts to standardize the definition of intestinal dysbiosis have been made, and indices such as alpha diversity, beta diversity, and the microbial dysbiosis index have been developed (13,14). Studies have revealed that dysbiosis is closely associated with the occurrence of the disease as well as disease activity (15-17). Although the definite causes of dysbiosis have not been elucidated, various factors, such as infection, inflammation, diet, drugs, host genetics, and familial transmission, are associated with dysbiosis (5,7,8,18).

Although dysbiosis is closely associated with the pathogenesis of IBD, the cause-and-effect relationship has not been fully elucidated (16,19). Commensal bacteria usually reside in the

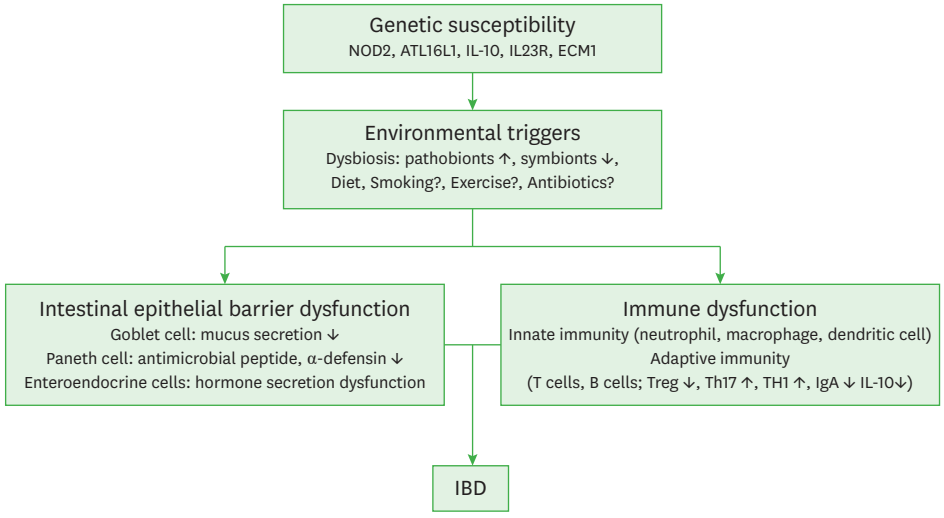

Figure 1. Pathogenesis of inflammatory bowel diseases.

outer mucus layer of the intestine (20). They play a substantial role in maintaining an intact mucosal barrier by interacting with the mucus layer and intestinal epithelium (20). It remains unclear whether mucosal barrier dysfunction precedes dysbiosis or vice versa. even though they are closely associated.

However, some pathogenic bacteria have the ability to disrupt and penetrate the intestinal mucosal barrier. Direct mucosal invasion by pathogenic bacteria or indirect mucosal injuries triggered by immunologic dysregulation followed by mucosal intolerance to various types of Ags generated during dysbiosis can cause intestinal inflammation (21). For example, adherent-invasive *Escherichia coli* (AIEC) disrupts the intact intestinal mucosa barrier by synthesizing alpha-hemolysin and then invades intestinal epithelial cells (22). This suggests that immunological or genetic factors as well as bacterial factors may be involved in the pathogenesis of IBD (17). More specifically, although *E. coli* and *Enterococcus faecalis* could not trigger intestinal inflammation in wild-type mice, they could trigger intestinal inflammation in IL $10^{-/-}$ mice in the cecum and distal colon, respectively (23). Previous studies have reported that a history of acute infectious gastroenteritis is associated with an increased occurrence of IBD (24-26). Both antibiotic use and the invasion of the injured intestinal mucosa by opportunistic pathogenic microorganisms during the acute stage of an intestinal infection might trigger the development of IBD in the future. In many studies, decreased microbial diversity has been observed in patients with IBD, including pediatric patients (10,27-29). A considerable decrease in microbes belonging to the phylum Firmicutes has been previously reported (30,31). In addition, notable changes in microbial diversity have been reported even in oral samples from pediatric patients (more specifically, a significant loss of Fusobacteria and Firmicutes was found in patients with CD, and a significant loss of Fusobacteria combined with a significant increase in Spirochaetes, Synergistetes, and Bacteroidetes was found in patients with UC) (27). Notably, gut microbiota diversity was also significantly affected by environmental factors (geography, ethnicity, and diet), bowel resection surgery, and disease activity. Specific changes in microbial composition, such as a decreased Firmicutes to Bacteroidetes ratio, were also reported (8,12,16,32-35). More specifically, it is known that the levels of *Faecalibacterium prausnitzii*, a butyrate-producing bacterium, are lower in patients with IBD, whereas levels of AIEC are higher in patients with IBD (16,18,33,36-38).

Immune system alterations and dysbiosis in IBD

Disturbances in the balance between the immune system and the gut microbiota are closely interconnected in the pathogenesis of IBD; however, the cause-and-effect relationship between them has not been elucidated (4,12,16).

The innate and adaptive immune systems are reciprocally associated with regulation of the gut microbiota (39-41). In the innate immune system, the dysfunction of pattern recognition receptors (PRRs), including nucleotide-binding oligomerization domain-like receptors (NLR) and TLRs, in cells such as granulocytes, macrophages, and dendritic cells, can result in microbial imbalances. The dysfunctional recognition of the peptidoglycans produced by gram-negative bacteria and disturbances in signaling pathways are particularly important in this process (12,16,39,42). Furthermore, some NLR proteins, such as nucleotide-binding oligomerization domain-containing protein (NOD)-, LRR-, and pyrin domain-containing 6 (NLRP6), help maintain a stable microbiota by secreting mucus and antimicrobial peptides via activating caspase 1, IL-1β, and IL-18 (12,16). Activated NLRP6 inflammasomes in the intestinal epithelium help in the secretion of IL-18 and antimicrobial peptides; however, in

dysbiosis they are suppressed by microbiota-derived metabolites. The resulting decrease in the levels of IL-18 and antimicrobial peptides can promote intestinal inflammation (12,43). Interestingly, NOD2 polymorphisms have been reported in patients with CD (16,44). In addition, the flagellin sensor TLR5 in dendritic and epithelial cells is stimulated to enhance antimicrobial peptide expression that prevents dysbiosis (12). Innate lymphoid cells regulate microbiota homeostasis by secreting cytokines such as IL-22, IFN-γ, and TNF (43). Dendritic cells and macrophages communicate with the gut microbiota and activate Th17 cells by stimulating the expression of IL-1β through MyD88 and NLRP3 (4,16,45). Some metabolites, such as butyrate, are also important mediators in the regulation of the gut microbiota by the innate immune system (16,40,46).

In the adaptive immune system, B cells play a central role in maintaining the intestinal microbiota, primarily by producing IgA (12,16,45). The commensal microbiota can induce the development of B cells that secrete IgA (12,45). Dysfunction in maintaining IgA, and the subsequent predominance of IgG instead of IgA, was a critical finding in patients with IBD (4). IgG predominance causes intestinal inflammation by activating the immune system. In particular, it stimulates the recruitment of inflammatory immune cells, complement activation, and cell lysis (4). In addition, T follicular helper cells also control the intestinal microbiota by promoting IgA production and expressing high levels of the inhibitory receptor PD-1, which regulates IgA and bacterial communities (12). The intestinal microbiota plays a substantial role in the development and regulation of the immune system, such as increasing the levels of Th17 cells and decreasing the levels of Tregs (4,30,40). Th17 cells, in particular, become pathogenic when stimulated by IL-12, IL-23, IL-1β, and TGF-β (45). The gut microbiota can also modulate the production of TGF-β, which affects the development of $Foxp3^+$ Tregs that can produce IL-10 (4). In addition, IL-22 can enhance the production of antimicrobial peptides and thus play a role in regulating the gut microbiota (45). Alternatively, the homeostasis between the gut microbiota and intestinal epithelium is maintained through T cells such as Tregs and Th17 cells, and in IBD, this homeostasis is disrupted (4,40). T cells that cannot tolerate commensal Ags can cause intestinal inflammation. In addition, the activity of cytokines such as IFN-γ and TNF is modulated by metabolites produced by the gut microbiota. SCFA such as butyrate, which are fermented from dietary fiber by commensal bacteria such as *Clostridia* spp., also control intestinal inflammation by modulating the activity of Tregs (4,16,30,40,43).

Microbiome and possible clinical biomarkers in the treatment of IBD

Microbiome-based techniques for the analysis of body fluids or wastes secreted by various body organs (urine, feces, saliva, serum, and bile acids) have been developed, and possible biomarkers have been identified for the diagnosis, response assessment, and detection of recurrence in IBD (10,47,48). A personalized treatment approach that combines modulating the gut microbiota and conventional treatments based on biomarkers is required to manage IBD using treat-to-target therapeutic strategies (10,48,49).

Microbial modulation to correct dysbiosis in IBD

Although the cause-and-effect relationship between dysbiosis and IBD remains unclear, microbial changes found in IBD are distinct and prominent (4,16). Correcting dysbiosis by selective engrafting of beneficial organisms while inhibiting harmful organisms is a reasonable approach. However, studies that attempted to correct dysbiosis using various IBD treatment options have shown inconclusive results (**Fig. 2**).

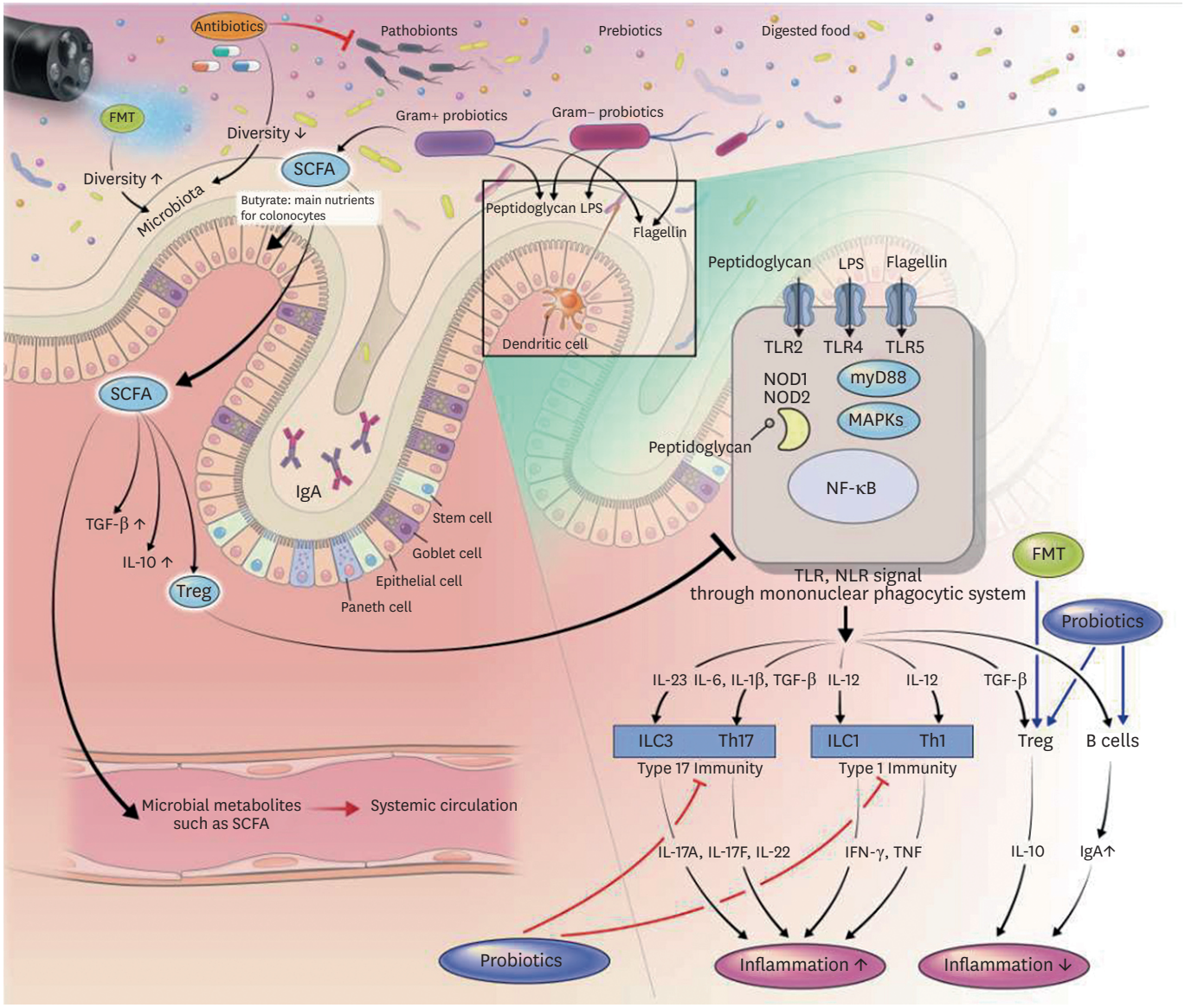

Figure 2. Microbial modulation by antibiotics, probiotics and fecal microbiota transplantation.

Immunological pathogenesis and microbial modulation

The administration of antibiotics suppresses microorganisms in the microbial ecosystem, but probiotics and FMT can be used to introduce a pool of microorganisms into the microbial ecosystem. Compositional changes in the microbial ecosystem induced by antibiotics, probiotics, and FMT can precede immunological alterations. Furthermore, numerous antibiotics, probiotics, and FMT combined with concomitant metabolic and signal transduction pathways are involved in changing the makeup of the gut microbiota and the immunological pathogenesis of IBD. Although microbial changes induced by using antibiotics, probiotics with or without prebiotics, and FMT in patients with IBD have been identified, elucidating its immunological pathogenesis has been difficult.

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ANTIBIOTICS AND MICROBIAL MODULATION

Use of antibiotics and changes in the microbiota

Antibiotics are commonly prescribed to treat infectious diseases (50). There are several classes of antibiotics with different spectra of action, pharmacokinetics, half-lives, and secretory passages (19). Antibiotics such as cephalosporin, metronidazole, and ciprofloxacin are commonly used to treat infectious intestinal diseases; however, their role in IBD is not well established, although they trigger changes in the intestinal microbiota (50).

Previous studies have shown that systemic antibiotics substantially affect the intestinal microbiota by decreasing its alpha and beta diversities in both human and mouse models (51-56). Antibiotics decrease the diversity of microbiota within several days, but recovery from the imbalance in the microbiota is highly dependent on host factors. Antibiotics can even result in irreversible changes in the intestinal microbiota (7).

Antibiotics must contact the mucus outer layer of the intestinal mucosa to affect commensal bacteria (20). Administration routes (intravenous or oral) may affect intestinal dysbiosis in different ways. For example, if antibiotics are administered orally, they might affect bacteria through their presence in the bloodstream (indirect route) or intestinal lumen (direct route), depending on the pharmacodynamics of each antibiotic. In addition, different classes of antibiotics may affect different types of commensal bacteria in the intestinal mucosa (50). For example, a short course of ciprofloxacin considerably changed the gut microbiota, decreasing the number of members of the phyla Firmicutes (Ruminococcaceae and Lachnospiraceae) and Bacteroidetes (54,57). Similarly, a seven-day course of clindamycin caused a decline in the number of organisms belonging to the phylum Bacteroidetes that persisted for at least two years, and a course of clarithromycin combined with metronidazole caused microbiota changes that lasted for about four years (57-59). Paradoxically, antibiotics can also cause *Clostridioides difficile*-associated diarrhea (CDAD) (50).

Relationship between the use of antibiotics and the future development of IBD

Exposure to antibiotics during childhood (particularly within one year of birth) increases the risk of IBD (13,60,61). A nationwide cohort study in Denmark showed that antibiotic use during childhood is a potential risk factor for the future development of IBD (60). Furthermore, a large case-control study in Sweden also suggested that the cumulative use of systemic antibiotics is associated with the development of IBD, and the risk increased with the use of broad-spectrum antibiotics. In this study, the use of cephalosporins was most closely associated with IBD development (62).

Antibiotics as a treatment option for patients with IBD

Previous systematic review and meta-analysis studies reported that a few antibiotics might be effective in managing IBD, particularly in patients with UC and UC-related pouchitis (**Table 1**). However, a Cochrane review reported that the effectiveness of antibiotic use in patients with active CD was only modest, and no meaningful clinical significance was shown (68). However, the studies used different types and regimens of antibiotics, and their heterogeneous outcomes make it difficult to reach definite conclusions (63).

Mycobacterium avium subspecies *paratuberculosis* (MAP) has been postulated to be associated with CD for a century. Therefore, studies on treatments that target MAP to manage CD have been carried out. However, no definite conclusions could be drawn from their results, although a

Table 1. Systematic review and meta-analysis studies on the use of antibiotics and anti-tuberculosis medications to treat inflammatory bowel disease

Disease	Number of studies (total patients enrolled*)	Treatment intervention	Duration of study	Control	Primary outcome	References
Antibiotics						
UC, CD, perianal fistula	Active CD (10 RCTs, n=1,160), perianal fistula (3 trials, n=123), Quiescent CD (3 RCTs, n=186), active UC (9 RCTs, n=662)	Antibiotics alone or in combination†	1–16 wk for active diseases, at least 6 months for diseases in remission	Placebo	- Induction of remission · Significant benefit in active CD (RR, 0.85; 95% CI, 0.73–0.99; p=0.03), in reducing fistula drainage (RR, 0.8; 95% CI, 0.66–0.98). · Significant benefit in inducing remission in UC (RR, 0.64; 95% CI, 0.43–0.96). - Maintenance of remission · Significant benefit in preventing CD relapse (RR, 0.62; 95% CI, 0.46–0.84).	(63)
Pouchitis (chronic refractory)	21 studies	Antibiotics with or without conventional treatment‡	2 wk–1 yr	Conventional treatment	- Induction of remission · Antibiotics significantly induced remission in patients with chronic pouchitis (remission rate, 74%; 95% CI, 56%–93%; p<0.001).	(64)
Pouchitis (acute and chronic)	15 RCTs (n=547)	Single or mixed antibiotics and single or mixed form of probiotics§	2 wk–24 mon	Budesonide enema or placebo	- Active pouchitis · Induction of remission: Induction of remission at 2 wk [100% (7/7) in ciprofloxacin group vs. 33% (3/9) in metronidazole group; RR, 2.68; 95% CI, 1.13–6.35; very low certainty evidence]. · Clinical response: Clinical improvement at 6 wk [50% (7/14) in metronidazole group vs. 58% (7/12) in budesonide enema group; RR, 0.86; 95% CI, 0.42–1.74; very low certainty evidence]. Clinical improvement at 4 wk [38% (3/8) in rifaximin group vs. 30% (3/10) in placebo group; RR, 1.25; 95% CI, 0.34–4.60; very low certainty evidence]. - Chronic pouchitis · Maintenance of remission: Maintenance of remission at 9 to 12 months [85% (34/40) in De Simone group vs. 3% (1/36) in placebo group; RR, 20.24; 95% CI, 4.28–95.81; 2 studies; low certainty evidence].	(65)
UC	12 RCTs (n=739)	Single or mixed antibiotics	5 days–6 mon	Placebo or no antibiotics	- Induction of remission · Statistically significant efficacy in inducing remission rate in patients with UC (random effect RR, 0.77; 95% CI, 0.60–0.98; p=0.03) or at 12 months after trials (fixed-effect RR, 0.83; 95% CI, 0.73–0.94; p=0.003).	(66)
UC	12 RCTs (n=847)	Antibiotics only or with standard regimen	At least 2 wk for induction and 3 mon for maintenance	Concurrent medications	- Induction of remission · No difference in failure to achieve clinical remission with high certainty evidence (RR, 0.88; 95% CI, 0.74–1.06). - Clinical response · No difference in failure to achieve clinical response with low certainty evidence (RR, 0.75; 95% CI, 0.47–1.22).	(67)
Pouchitis	18 RCTs	Antibiotics	3 wk–24 mon	Placebo	- Induction of remission · Acute pouchitis: Rifaximin: the best antibiotic for acute pouchitis. Ciprofloxacin ranked highest against metronidazole. · Chronic pouchitis: Metronidazole followed by probiotics was effective in inducing remission. Metronidazole: the highest adverse events. - Maintenance of remission · Probiotics proved superior to placebo in the prevention of pouchitis development.	(56)

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double-blind, placebo-controlled, multicenter randomized controlled trial (RCT) is ongoing to assess anti-MAP therapy in patients with CD (71). Similarly, attempts at using anti-tuberculosis medications to control MAP have been made for a long time (69). In a Cochrane library review published in 2016, it was concluded that anti-tuberculosis medications might be beneficial over placebo in preventing relapse in patients with CD, although the significance was uncertain (70). Only four placebo-controlled RCTs were included in the review, and the

Table 1. (Continued) Systematic review and meta-analysis studies on the use of antibiotics and anti-tuberculosis medications to treat inflammatory bowel disease

Disease	Number of studies (total patients enrolled*)	Treatment intervention	Duration of study	Control	Primary outcome	References
CD	13 RCTs (n=1,303)	Single or mixed antibiotics with or without conventional treatment	6 wk–3 yr	Placebo with or without conventional treatment	- Induction of remission · Failure to achieve remission at 6–10 wk [55% (289/524) of antibiotics group vs. 64% (149/231) of placebo group; RR, 0.86; 95% CI, 0.76–0.98; 7 studies; high certainty evidence]. - Clinical response · Failure to achieve a clinical response at 10–14 wk [41% (174/428) of antibiotics group vs. 49% (93/189) of placebo group; RR, 0.77; 95% CI, 0.64–0.93; 5 studies; moderate certainty evidence]. - Maintenance of remission · Uncertain effect of antibiotics on relapse at 52 wk [45% (37/83) of antibiotics group vs. 57% (41/72) of placebo group; RR, 0.87; 95% CI, 0.52–1.47; 2 studies; low certainty evidence].	(68)
Anti-tuberculous therapy						
CD	8 randomized trials (n=15–126)	Antimycobacterial therapy with or without standard treatment	6–24 mon	Placebo or standard treatment	- Maintenance of remission · Antimycobacterial therapy versus control: 3.37 (95% CI, 1.38–8.24). · Antimycobacterial therapy with standard therapy versus standard therapy alone: 0.69 (95% CI, 0.39–1.21).	(69)
CD (quiescent)	4 RCTs (n=206)	Anti-tuberculous therapy	6–36 mon	Placebo or active therapy	- Maintenance of remission · A statistically significant difference in relapse rates at 9 months to 2 years favoring anti-tuberculous therapy over placebo [39% (44/112) in anti-tuberculosis group vs. 67% (63/94) in placebo group; RR, 0.58; 95% CI, 0.45–0.75). · More frequent adverse events in the anti-tuberculous therapy group (37/159) compared to the placebo group (14/163) with a pooled RR of 2.57 (95% CI, 1.45–4.55).	(70)

*Total number of patients enrolled or minimum–maximum number of patients among enrolled studies; †anti-tuberculosis therapy, macrolides, fluoroquinolones, 5-nitroimidazoles, and rifaximin; ‡biologics, steroids, bismuth, elemental diet, tacrolimus, FMT; §VSL#3, *Bifidobacterium longum*, *Clostridium butyricum* MIYAIRI.

quality of the study, in terms of the number of patients and protocols, was insufficient to conclude that anti-tuberculosis medications were efficacious in preventing CD relapse. Anti-tuberculosis medications are not commonly used to manage IBD because of the burden of side effects (70). **Table 1** summarizes the systematic review and meta-analysis studies on the use of antibiotics and anti-tuberculosis medications in the treatment of IBD.

Although it is well known that antibiotics disturb the intestinal microbiota, the details of intestinal microbial changes associated with the use of antibiotics in IBD cannot be easily investigated (63,72,73). However, whether the improvement in clinical outcomes after treatment with antibiotics is due to the correction of dysbiosis in patients with IBD remains unclear.

Immunological pathogenesis when the use of antibiotics affects microbiota modulation

Generally, anaerobic bacteria play a crucial role in the development of the innate immune system. However, antibiotics reduce the diversity and abundance of intestinal microbiota, resulting in the loss of colonization resistance (19,58). Although the full immunological pathogenesis remains to be elucidated, antibiotics might disturb the immunological balance by contributing to the loss of colonization resistance, which is maintained by antimicrobial peptide production, bile acid metabolism, epithelial barrier maintenance, bacteriocin production, nutrients metabolic pathways and type VI secretion systems, which can act as an antimicrobial toxin (19). In addition, antibiotics could trigger intestinal inflammation by generating reactive nitrogen and oxygen species (50). Furthermore, broad-spectrum

antibiotics significantly decreased $CD4^+$ Th lymphocytes and the production of cytokines such as IL-10, IL-17, IL-22, and IFN-γ in mice (74).

PROBIOTICS, PREBIOTICS, SYNBIOTICS, AND MICROBIAL MODULATION

Microbial modulation using probiotics in the general population

Probiotics are microorganisms that beneficially affect the host (75). Probiotics, administered with or without prebiotics, are one of the most commonly used medications on the market. However, previous RCTs have not substantially proven their clinical effectiveness to justify their routine use. Recent guidelines recommend that a few strains of probiotics may be useful in limited settings, such as the prevention of *Clostridioides difficile* infection (CDI) in patients who are on antibiotics or in preterm, low-birth-weight infants with necrotizing enterocolitis, and they may also be used to prevent the relapse of UC-related pouchitis (76). Furthermore, the use of probiotics is not recommended for children with acute gastroenteritis (76). Nevertheless, some strains among the numerous kinds of probiotics have shown promising outcomes and rarely produce side effects. Recent advances in molecular biology techniques, such as 16S ribosomal RNA sequencing and NGS, have helped in elucidating the role and pathophysiology of microbiomes, including probiotics, in incurable human diseases such as IBD (77). The diversity of the microbiota is significantly associated with the stability of microbial communities (78). Probiotics have been used to diversify the microbiota, but their clinical effectiveness is inconsistent among individuals. Furthermore, the specific changes in the microbiota that are associated with the dosage, regimen, or class of probiotics are not well understood. Interestingly, the empirical administration of probiotics results in mucosal colonization resistance, the extent of which is dependent on the person, strain, and region (79). For example, daily administration of *Lactobacillus rhamnosus* increased the abundance, stability, and evenness of the microbial community in infants (80). In contrast, the characteristics of the microbiota found in feces after the daily administration of a milk product containing *Lactobacillus rhamnosus* DR20 suggested that only transient colonization had occurred (81). Another study found that perinatal maternal probiotic supplementation did not alter microbial diversity in children (82). In addition, the engraftment of *Bifidobacterium longum* AH1206 has been found to depend on individual microbial features (83). Furthermore, even if microbial compositional changes or increased microbial concentrations in the intestines or feces are induced by exogenous administration of probiotics, their biological effects on the gut microbiota and host system are not evident. Moreover, it is not well understood how long the effects of probiotics persist.

Microbial modulation using probiotics in diseases other than IBD

Microbial modulation with probiotics has been studied for other diseases, including irritable bowel syndrome (IBS), obesity, and allergic diseases (84-87). For example, treatment with a multispecies probiotic mixture for eight weeks stabilized the intestinal microbiota in patients with IBS (85). Similarly, *Bifidobacterium animalis* in fermented milk improved symptoms in patients with IBS, and an increase in SCFA production and a decrease in pathogenic bacterial products (88). In contrast, *Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* Bi-07 administration did not notably affect the microbial diversity or composition in the feces of infants with atopic dermatitis (87). Intestinal microbial modulation by probiotics might also influence systemic diseases, possibly by affecting the expression or activity of immunological factors. The gut microbiota can also systemically influence the host by releasing microbiome-

associated metabolites that can translocate through the intestinal epithelium into the circulatory system. After these metabolites enter the circulatory system, they can reach and possibly affect other organs such as the liver, brain, and lungs, which exert systemic effects (12,89). Specific strains of probiotics, such as *Lactobacillus, Bifidobacterium, Akkermansia muciniphila, F. prausnitzii*, and the yeast *Saccharomyces boulardii*, produce SCFAs that regulate the expression of genes involved in the secretion of gut hormones and maintenance of Tregs after activating G-protein-coupled receptors (90). In addition, some probiotics can produce small extracellular vesicles, which may be useful in maintaining gut epithelial layers by mediating bacteria-host interactions (91).

Probiotics as a treatment option for IBD

Probiotics have been investigated as a possible treatment option for IBD, particularly because they rarely have side effects. However, only a few studies have proven that probiotics have beneficial effects in clinical practice. A few probiotics have been shown to be effective, paricularly in patients with UC, rather than CD (5,7,49,92-97). Systematic review and meta-analysis studies reported that some types of probiotics containing *Bifidobacterium*, such as VSL#3, were effective, particularly in inducing remission in patients with active UC and in preventing the relapse of pouchitis (**Table 2**). In addition, recent Cochrane systematic reviews have suggested that probiotics could induce clinical remission in patients with active UC at rates comparable with those of 5-aminosalicylic acids (5-ASA), with low certainty of evidence. Their effectiveness in the maintenance of remission in UC and CD was unclear because of the lack of well-designed RCTs (104-106).

Microbial modulation using probiotics in IBD

Few clinical studies have focused on microbial modulation using probiotics to correct dysbiosis in IBD, as there is insufficient evidence on the clinical effectiveness of probiotics in IBD management (49,107). Studies on microbial modulation by probiotics in IBD are particularly complex because it is difficult to prove the direct effectiveness of each probiotic in modulating intestinal microbial ecosystems that have already been shaped by numerous species of gut microorganisms. Furthermore, detailed information on the sequential changes in the concentration of the probiotics and their metabolites, such as SCFA, in the intestine and feces depending on each probiotic regimen (delivery route, concentration, single or mixed) is required to definitively prove the effectiveness and cause-and-effect relationship of probiotics and IBD. Furthermore, even when their effectiveness is shown, the duration of the effectiveness and long-term safety also need to be evaluated. Previous studies have demonstrated effectiveness of microbial modulation with probiotics in relieving intestinal inflammation (49,108-112). In an animal study, *Lactobacillus reuteri* increased microbial diversity and community evenness in mice 24 h after administration (113). Clinical studies have analyzed detailed microbial changes in the intestine or feces following probiotic administration (114-118). For example, in a pilot study, *Bifidobacteria*-fermented milk improved clinical outcomes, with significantly increased concentrations of SCFA and *Bifidobacterium* species, particularly *Bifidobacterium breve* and *Bifidobacterium pseudocatenulatum*. There was also an insignificant decrease in the number of *Bacteroides fragilis* in patients with active UC (116). Furthermore, the number of *Bifidobacterium* species significantly decreased in the relapsed group compared to the remission group, although administration of *B. breve* Yakult with fermented milk did not show any clinical benefit or microbiota changes, except for insignificant changes in the level of *Clostridium leptum* in patients with UC (115). In contrast, *B. breve* Yakult administered with prebiotics significantly improved clinical parameters while decreasing fecal pH and the number of members of the family *Bacteroidaceae* present

Table 2. Systematic review and meta-analysis studies on the use probiotics and synbiotics to treat inflammatory bowel disease

Disease	Number of studies (total patients enrolled*)	Treatment intervention	Duration of study	Control	Primary outcome	References
Probiotics, synbiotics						
UC, pouchitis, CD	43 trials for qualitative synthesis, 15 trials for quantitative synthesis (meta-analysis) (n=1–327)	Single or mixed form of probiotics, synbiotics	4–52 wk	Placebo or conventional treatment	- Induction of remission · 2.70 (95% CI, 0.47–15.33) for inducing remission in active UC with Bifido-fermented milk. · 1.88 (95% CI, 0.96–3.67) for inducing remission in active UC with VSL#3 - Maintenance of remission · 1.08 (95% CI, 0.86–1.37) for preventing relapses in inactive UC with *Escherichia coli* Nissle 1917. · 0.17 (95% CI, 0.09–0.33) for preventing relapses in inactive UC/IPAA patients with VSL#3. · Preventing endoscopic recurrences in inactive CD (*Lactobacillus rhamnosus* GG, 1.21; 95% CI, 0.57–2.57; *Lactobacillus johnsonii*, 0.93; 95% CI, 0.63–1.38). · No evidence to support the use of probiotics in CD.	(98)
UC, pouchitis, CD	23 RCTs (n=18–327)	Single or mixed form of probiotics, with or without conventional treatment	1–24 mon	Placebo or active treatment	- Induction of remission · Significantly increased remission rates in active UC (p=0.01; RR, 1.51) · Significantly higher remission rates in patients with active UC treated with probiotics (p<0.0001; RR, 1.80) · Significantly increased remission rates with only VSL#3 in active UC (p=0.004; RR, 1.74). - Maintenance of remission · Significantly reduced clinical relapse rates for maintaining remission with VSL#3 in patients with pouchitis (p<0.00001; RR, 0.18).	(99)
UC, CD	22 RCTs (n=20–327)	Single or mixed form of probiotics	7–52 wk	5-ASA or placebo	- Induction of remission · No benefit over placebo in active UC (RR of failure to achieve remission, 0.86; 95% CI, 0.68–1.08). · Possible effectiveness of VSL#3 in active UC (RR, 0.74; 95% CI, 0.63–0.87). - Maintenance of remission · Similar effectiveness to 5-ASA in preventing UC relapse (RR, 1.02; 95% CI, 0.85–1.23). · No benefit in treatment and prevention of relapse in CD.	(94)
UC, CD	9 RCTs for CD, 18 RCTs for UC (n=11–187)	Single or mixed form of probiotics or synbiotics with or without standard treatment (antibiotics or 5-ASA)	4–52 wk	Placebo	- Induction of remission · Significant effects on UC (p=0.007; RR, 0.88), especially VSL#3 (p<0.01; RR, 0.47) and synbiotics (*Lactobacillus* with prebiotics) (p=0.03; RR, 1.16). · No significant effects on CD (95% CI, 0.7–1.0; p=0.07; RR, 0.87) but possible effectiveness of probiotics mixture (*S. boulardii*, *Lactobacillus* and VSL#3) in CD (p=0.057; RR, 0.85).	(100)
UC, CD	32 RCTs (n=11–360)	Single or mixed form of probiotics, synbiotics with or without conventional treatment	4–52 wk	Placebo or active treatment	- Induction and maintenance of remission · Probiotics, prebiotics and synbiotics can induce/maintain remission and reduce UC disease activity index (RR, 1.13; 95% CI, 1.02–1.26; p<0.05). · Synbiotics are more effective in the treatment of IBD (especially UC). · *Lactobacillus* and *Bifidobacterium* or more than one strain are more likely to be beneficial for IBD remission. · The dose of 10^{10}–10^{12} CFU/day may be a reference range. - Microbial changes · Probiotic supplements can increase the number of beneficial bacteria (especially *Bifidobacteria*).	(101)
UC	18 RCTs (n=18–327)	Single or mixed form of probiotics, only prebiotics (1 RCT), only synbiotics (1 RCT)	Variable	Placebo or conventional treatment	- Induction of remission · *Bifidobacteria*-containing probiotics (RR, 1.73; 95% CI, 1.23–2.43; p=0.002). - Maintenance of remission · No significant effects in the maintenance of remission for placebo-controlled or mesalazine-controlled studies.	(102)

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Table 2. (Continued) Systematic review and meta-analysis studies on the use probiotics and synbiotics to treat inflammatory bowel disease

Disease	Number of studies (total patients enrolled*)	Treatment intervention	Duration of study	Control	Primary outcome	References
UC	60 RCTs (n=4,954)	BTV with ASA	28–90 days	5-ASA	- Induction of remission · BTV plus ASA rather than ASA alone significantly improved the clinical remission rate (RR 1.23, 95% CI 1.20–1.26; p<0.00001) - Maintenance of remission · BTV plus ASA rather than ASA alone significantly reduced the relapse rate (RR 0.34, 95% CI 0.18–0.62; p=0.0005); and adverse effect rate (RR 0.66, 95% CI 0.53–0.82; p=0.0002). - Biomarkers · Reduced levels of TNF-α, IL-6, IL-8, CRP, hCRP, ESR, and malondialdehyde in BTV plus ASA group. · Increased levels of IL-10, CD3+, CD4+, and superoxide dismutase in BTV plus ASA group.	(103)
UC in remission	12 studies (n=1,473)	Probiotics (7 studies with a single bacterial strain, and 5 studies with multiple strains with or without 5-ASA	12–52 wk	Placebo, no treatment, or any other intervention	- Maintenance of remission · Uncertain in preventing clinical relapse (probiotics vs. placebo; RR 0.87, 95% CI 0.63–1.18; 4 studies, 361 participants; very low-certainty evidence) and in maintenance of clinical remission (probiotics vs. placebo; RR 1.16, 95% CI 0.98–1.37; 2 studies, 141 participants; very low-certainty evidence) · Little or no difference in clinical relapse (probiotics vs. 5-ASA; RR 1.01, 95% CI 0.84–1.22; 2 studies, 452 participants; low-certainty evidence) and maintenance of clinical remission (probiotics vs. 5-ASA; RR 1.06, 95% CI 0.90–1.25; 1 study, 125 participants; low-certainty evidence) · Uncertain if there is any difference in clinical relapse (probiotics with 5-ASA vs. 5-ASA alone; RR 1.11, 95% CI 0.66–1.87; 2 studies, 242 participants; very low-certainty evidence) · Little or no difference in maintenance of remission (probiotics with 5-ASA vs. 5-ASA alone; RR 1.05, 95% CI 0.89–1.24; 1 study, 122 participants; low-certainty evidence) · No serious adverse events or withdrawals	(104)
UC, active	14 studies (n=865)	Probiotics with or without 5-ASA (7 studies with a single probiotic strain and 7 with a mixture of strains)	2–52 wk	Placebo or 5-ASA	- Induction of remission · Induction of clinical remission (probiotics vs. placebo; RR 1.73, 95% CI 1.19–2.54; 9 studies, 594 participants; low-certainty evidence) · Improvement in clinical disease scores (probiotics vs. placebo; RR 2.29, 95% CI 1.13–4.63; 2 studies, 54 participants) · Little or no difference in the induction of remission (probiotics vs. 5-ASA; RR 0.92, 95% CI 0.73–1.16; 1 study, 116 participants; low-certainty evidence) · Slight improvement in the induction of remission (probiotics with 5-ASA vs. 5-ASA alone; RR 1.22, 95% CI 1.01–1.47; 1 study, 84 participants; low-certainty evidence)	(105)
CD, active	2 RCTs (n=11, 35)	Single probiotics (*Lactobacillus rhamnosus* GG) and synbiotics (*Bifidobacterium longum* with prebiotics)	24 wk–6 mon	Placebo or any other non-probiotic intervention	- Induction of remission · No evidence of a difference between the probiotics and placebo for the induction of remission in CD (RR 1.06, 95% CI 0.65–1.71; 2 studies, 46 participants) after six months · No difference in adverse events between probiotics and placebo (RR 2.55, 95% CI 0.11–58.60; 2 studies, 46 participants)	(106)

*Total number of patients enrolled or minimum–maximum number of patients per study.

in the feces of patients with UC (117). Probiotics (*Bifidobacterium lactobacillus* triple tablets) administered with glucocorticoids also showed clinical efficacy and decreased the levels of yeast, enterococci, and peptococci, and increased the level of *Lactobacillus* in patients with CD (114). The administration of Bifid triple viable capsules (1.26 g/d for eight weeks) increased the concentration of *Lactobacilli* and *Bifidobacteria* in the feces of patients with UC and decreased the number of inflammatory markers and the likelihood of clinical relapse (118).

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Theoretically, if antibiotics can be used to reduce of pathobiont levels and probiotics can be used to increase the levels of beneficial microbes, intestinal dysbiosis might be better modulated. For example, concurrent administration of VSL#3 and clindamycin showed a stabilizing effect on the intestinal microbiota by preventing antibiotic-related disturbances (119). In contrast, dysbiosis induced by antibiotics can be corrected using FMT but not with probiotics (120).

Immunological pathogenesis and microbiota modulation using probiotics

When probiotics encounter the intestinal epithelial layer and the pre-existing microbial communities in the host intestine, they interact with these ecosystems through immunological pathways (121). Although the function and mechanism of probiotic bacteria differ from species to species, they primarily affect intestinal epithelial cells and immune cells through common pathways, including those that involve soluble factors such as cytokines and metabolites. More specifically, probiotic bacteria have surface components, such as surface layer proteins, capsular polysaccharides, flagella, fimbriae, and pili. Combinations of these elements are known as microbe-associated molecular patterns, and they bind to PRRs such as NLRs or TLRs (96). The flagellin found in symbiotic microbiota can induce inflammation only when it contacts the basolateral membrane of the intestinal epithelium (122). Furthermore, the tight adhesion pili of *Bifidobacterium* stimulate the proliferation of cells in the intestinal mucosa (123). In addition, capsular polysaccharides play a role in the adaptation and colonization of the intestinal microbial ecosystem (124). In probiotic bacteria, these surface molecules are expressed by genes that encode soluble factors such as cytokines, chemokines, and antimicrobial peptides. These genes are activated when bound PRRs and stimulate the NF-κB and MAPK signaling pathways. In this way, they maintain the intestinal barrier by preserving tight junctions and promoting mucus production by the goblet cells. In addition, probiotic bacteria can suppress pathogens by producing IgA and β-defensins (96,112).

Prebiotics and synbiotics

Prebiotics are defined as substrates that are selectively utilized by host microorganisms and confer health benefits (125). The microorganisms in the host metabolize them into SCFAs such as acetate, propionate, and butyrate, all of which have beneficial effects on the intestinal microbiome (95). Prebiotics are usually combined with probiotics in clinical trials, and a few clinical studies have evaluated the effectiveness of administering prebiotics alone, with inconsistent results (126-129). Synbiotics are combinations of prebiotics and probiotics, which are designed with the goal of maximizing their synergetic effects. The administration of synbiotics is considered particularly helpful in the management of IBD because it combines the advantages of probiotics and prebiotics and has partially beneficial clinical outcomes. A recent systematic review and meta-analysis study reported that synbiotics were more effective than probiotics alone in the treatment of IBD, particularly for UC (101). However, further studies are required to determine the effectiveness and safety of synbiotics.

FECAL MICROBIOTA TRANSPLANTATION AND MICROBIAL MODULATION

FMT and its current use

FMT is a procedure in which stool from healthy donors is infused into recipients. However, there are no standardized, unified protocols (administration routes, methods of stool preparation or storage, donor selection, etc.) (130). Recently, FMT has received more

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attention, but the only formal indication for its use is for the treatment of recurrent or refractory CDAD (131,132). In an animal study, antibiotic (ampicillin) treatment for one week caused a significant decrease in microbial alpha diversity, and discontinuing the administration of antibiotics could not reverse this outcome. However, after FMT, this disruption of the intestinal microbial community was significantly reversed. It appears that FMT could be used to help restore the balance of the intestinal microbial ecosystem after disturbances caused by the administration of antibiotics to patients with CDAD (132,133).

FMT as a treatment option in patients with IBD

Considering that dysbiosis is associated with IBD, correcting it using healthy donor FMT has been attempted. However, the results have been inconsistent in patients with IBD. Systematic reviews and meta-analysis studies have shown that FMT can have beneficial effects in patients with UC, CDI, and IBD. However, in patients with CD, the beneficial effects were inconsistent (**Table 3**). A Cochrane review published in 2018 suggested that FMT improved clinical and endoscopic remission with low certainty evidence (142).

Microbial modulation using FMT in patients with IBD

There have been several attempts to use FMT to modulate microbial dysbiosis associated with various intestinal diseases. Previous studies have shown that FMT reversed dysbiosis in patients with IBD by increasing the number of beneficial organisms and decreasing the

Table 3. Systematic review and meta-analysis studies on the use of fecal microbiota implantation to treat inflammatory bowel diseases

Category of diseases	Number of studies (total patients enrolled*)	Treatment regimen	Study duration	Control	Primary outcomes	References
IBD, infectious diarrhea in IBD	17 studies including 9 case series/case reports for IBD, 8 for infectious diarrhea in IBD (n=41 for IBD, n=27 for UC, n=12 for CD, n=2 for IBD unclassified)	FMT	2 wk–13 yr	Placebo	- Induction of remission · Disease remission (15/24: 62.5%). · Resolution of CDI (15/15: 100%). - Clinical response · Reduction of symptoms (19/25: 76.0%). · Cessation of IBD medications (13/17: 76.5%).	(134)
IBD (UC, CD, unclassified)	18 studies including 9 cohort studies, 8 case studies and 1 RCT (n=122; n=79 for UC, n=39 for CD, n=4 for IBD unclassified)	FMT	1 mon–13 yr (case studies), (4 wk–over 1 yr (cohort study), 7 wk (1 RCT)	Placebo (water enema)	- Induction of remission · CR: 45.0% (54/119). · Pooled proportion of patients that achieved CR was 36.2% (the cohort studies; 95% CI, 17.4%–60.4%; p=0.011). · Pooled estimate of CR: 22.0% (95% CI, 10.4%–40.8%; p=0.37) for UC and 60.5% (95% CI, 28.4%–85.6%; p=0.05) for CD. - Microbial changes · Six studies performed microbiota analysis which investigated the association among specific microbiota change, clinical response, and disease activities. · Inconsistent microbiota changes without definite conclusions.	(135)
IBD, CDI	67 studies including CDI of 76.3% and IBD of 13.2% (n=844)	FMT	Variable	Placebo	- Induction of remission · 90.7% of patients with refractory/relapsing CDI were cured and 78.4% of patients with IBD were in remission after FMT.	(136)
IBD, CDI	168 studies (CDI=108, IBD=31)	Single or multiple FMT	Variable	Placebo	- Induction of remission · Final cure rate for CDI: 95.6% (95% CI, 93.9%–97.1%). · Final remission rates for UC and CD: 39.6% (95% CI, 25.4%–54.6%) and 47.5% (95% CI, 29.4%–65.8%), respectively. · Cure rates in CDI and final remission rates for CD and UC were comparable across all routes of FMT administration. · Overall adverse event incidence was <1%, mostly gastrointestinal-related.	(137)

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Table 3. (Continued) Systematic review and meta-analysis studies on the use of fecal microbiota implantation to treat inflammatory bowel diseases

Category of diseases	Number of studies (total patients enrolled*)	Treatment regimen	Study duration	Control	Primary outcomes	References
CDI in IBD	9 cohort studies (Total n=346, n=12–67)	FMT	7 days–over 1 yr	CDI patients without IBD	- Induction of remission · The initial cure rate: 81% (95% CI, 76%–85%). · The overall cure rate: 89% (95% CI, 83%–93%). · No significant difference in the CDI cure rate after FMT in patients with and without IBD (RR, 0.92; 95% CI, 0.81–1.05). · Similar CDI treatment effects after FMT in patients with CD and UC (p=0.1804). - Maintenance of remission · The recurrence rate: 19% (95% CI, 13%–27%).	(138)
CDI in IBD	n=457	Single or multiple FMT	Variable	Placebo	- Induction of remission · CDI resolution after first FMT with a pooled cure rate of 78% (363/457) (95% CI, 73%–83%). Overall pooled rate cure rate with single and multiple FMTs was 88% (95% CI, 81%–94%). · FMT is a highly effective therapy for preventing recurrent CDI in patients with IBD. · Patients who fail a single FMT may benefit from multiple FMTs.	(139)
UC, CD, pouchitis	53 studies (41 for UC, 11 for CD, 4 for pouchitis)	FMT	1 wk–13 yr	Placebo	- Induction of clinical remission · UC, 36% (201/555); CD, 50.5% (42/83); pouchitis, 21.5% (5/23). · The pooled proportion achieving CR: 33% (95% CI, 23%–43%) for UC and 52% (95% CI, 31%–72%) for CD. · Significant benefit in CR (pooled OR, 2.89; 95% CI, 1.36–6.13; p=0.006; 4 RCTs in UC). · Remission in UC improved with increased number of FMT infusions and lower gastrointestinal tract administration. - Microbial changes · Microbiota analysis was performed in 24 studies, with many identifying increased diversity and a shift in recipient microbiota profile towards the donor post-FMT.	(140)
IBD (UC, CD, mixed)	29 studies (n=514)	FMT	4 wk–3 yr	Placebo, autologous FMT, or standard therapy	- Clinical response · The pooled rate of IBD worsening was 14.9% (95% CI, 10.0%–21.0%). · The higher pooled rate of worsening in IBD activity without statistical significance (FMT for CDI: 22.7% [95% CI, 13.0%–36.0%] vs. FMT for IBD: 11.1% [95% CI, 7.0%–17.0%]) · A marginal risk of worsening in IBD activity 4.6% (95% CI, 1.8%–11%).	(141)
UC, CD	4 randomized or non-randomized studies with a control arm (n=277)	FMT containing distal gut microbiota from a healthy donor	7 wk–12 mon	Participants without FMT or with placebo or autologous FMT or no intervention.	No eligible trials about the treatment of CD. Most participants had mild to moderate UC. - Induction of remission · Improved CR rates at 8 wk with FMT by two-fold in patients with UC (37% [52/140] in FMT vs. 18% [24/137] in control; RR, 2.03; 95% CI, 1.07–3.86). · Serious adverse event (7% [10/140] in FMT group vs. 5% [7/137] in control group; RR, 1.40; 95% CI, 0.55–3.58; 4 studies). · Endoscopic remission at 8 wk favoring FMT (30% [35/117] in FMT group vs. 10% [11/112] in control group; RR, 2.96; 95% CI, 1.60–5.48; 3 studies). - Maintenance of remission · Relapse at 12 wk (0% [0/7] in FMT group vs. 20% in control group; RR, 0.28; 95% CI, 0.02–4.98; 17 participants, very low certainty evidence; 1 study). - Clinical response · Clinical response at 8 wk (49% [68/140] in FMT group vs. 28% [38/137] in control group; RR, 1.70; 95% CI, 0.98–2.95; 4 studies).	(142)

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Table 3. (Continued) Systematic review and meta-analysis studies on the use of fecal microbiota implantation to treat inflammatory bowel diseases

Category of diseases	Number of studies (total patients enrolled*)	Treatment regimen	Study duration	Control	Primary outcomes	References
CD (active)	15 studies; 13 cohorts and 2 RCTs	Single-dose or multi-dose FMT with or without pre-FMT antibiotics	4–52 wk	Placebo	- Clinical response · Clinical response rates in early follow up were higher following multiple FMT than with single FMT. · FMT dose did not appear to influence clinical outcomes, nor did whether FMT was fresh or frozen. · The benefit of pre-FMT antibiotic administration was not able to be determined due to the limited number of patients and varying antibiotic regimens. · No serious adverse events.	(143)
CD (Fistulizing)	27 trials	Combination therapy with TNF antagonists and antibiotics	4–54 wk	TNF antagonist alone.	- Induction of remission · The efficacy of TNF antagonists with moderate-quality evidence (RR, 2.01; 95% CI, 1.36–2.97), particularly infliximab, ustekinumab (RR, 1.77; 95% CI, 0.93–3.37), and mesenchymal stem cell therapy (RR, 1.31; 95% CI, 0.98–1.73) for induction of fistula remission. · The efficacy of combination therapy with TNF antagonists and antibiotics vs. a TNF antagonist alone with low-quality evidence.	(144)
UC (active)	4 RCTs (n=277)	FMT	7–12 wk	Placebo enema, autologous stool	- Induction of remission · Higher combined clinical and endoscopic remission with FMT compared with placebo (RR for UC not in remission, 0.80; 95% CI, 0.71–0.89) with a number needed to treat of 5 (95% CI, 4–10). · No statistically significant increase in serious adverse events with FMT compared with controls (RR adverse event, 1.4; 95% CI, 0.55–3.58).	(145)
UC (active)	14 cohort studies and 4 RCTs	FMT	1–72 mon	Placebo (autologous stool or water)	- Induction of remission · Higher CR in donor FMT group (39/140 [28%] in donor FMT group vs. 13/137 [9%] in placebo group; OR, 3.67; 95% CI, 1.82–7.39; p<0.01). · In cohort studies, 39 of 168 (24%; 95% CI, 11%–40%) achieved CR. - Clinical response · Higher clinical response in donor FMT group (69/140 [49%] in donor FMT group vs. 38/137 [28%] in placebo group; OR, 2.48; 95% CI, 1.18–5.21; p=0.02).	(146)
UC (active)	26 studies	FMT	2 wk–12 mon		FMT significantly improved in patients with UC. - Induction of remission · CR for active UC (OR, 3.634; 95% CI, 1.940–6.808). · Endoscopic remission (OR, 4.431; 95% CI, 1.901–10.324). · Serious adverse events were more often reported in control group (n=43) compared with FMT group (n=26). - Clinical response · Clinical response (OR, 2.634; 95% CI, 1.441–4.815; p=0.002).	(147)

*Total number of patients enrolled or minimum–maximum number of patients per study.

number of harmful ones while achieving a microbial composition that resembles that of healthy donors (30). Kao et al. (15) reported that FMT corrected dysbiosis and induced clinical remission in patients with CD. In a study that evaluated five patients with UC, only one patient showed a clinical response (Mayo score from 11 to 6) after 12 weeks of FMT infusion, with successful colonization by *F. prausnitzii, Rosebura faecis,* and *Bacteroides ovatus* (148). In contrast, FMT did not lead to clinical remission at 90 days in six patients with chronic refractory UC despite a transient increase in the diversity of the gut microbiota (a decrease in *Proteobacteria* including *Enterobacteriaceae* and an increase in *Bacteroidetes* and *Firmicutes*) (149). In addition, in an RCT for patients with mild to moderate UC, FMT was not statistically effective in inducing clinical and endoscopic remission, although there were some distinctive microbiota

changes in responders. In particular, the microbial diversity increased in both richness and evenness in all responders but did not significantly change in non-responders (a regain of *Clostridium* clusters IV, XIVa, and XVIII and reduction in *Bacteroidetes*) (150). Similarly, in a randomized placebo-controlled study, FMT reversed the altered microbiota composition observed in patients with UC, possibly by stimulating the production of SCFAs (151). Notably, in a multicenter, double-blind, randomized, placebo-controlled trial in Australia, intensive-dosing, multi-donor FMT induced clinical remission and endoscopic improvement at week eight in patients with active UC, and this was accompanied by distinct microbial changes, such as an increase in operational taxonomic units and phylogenetic diversity as early as week four. *Parabacteroides* spp., *Barnesiella* spp., *Clostridium* cluster IV, and *Ruminococcus* spp. were associated with remission, whereas *Fusobacterium* spp. and *Sutterella* spp. were associated with a lack of remission (152). In addition to bacterial dysbiosis, fungal dysbiosis was associated with reduced FMT efficacy, suggesting that fungi are also included in the intestinal ecosystem (153). With the development of microbial techniques and the accumulation of data from multiple studies, personalized combination regimens of probiotics and FMT have recently been designed (154).

Immunological pathogenesis and microbiota modulation by FMT

FMT increases the diversity of intestinal microbiota by reducing imbalances in the immune system, although the duration of the effectiveness of FMT has not been determined (155,156). Notably, the pre-FMT administration of antibiotics significantly increased the fraction of donor strains after FMT (157). Considering that FMT is a transfer of fresh stool (intestinal microbiota ecosystem: the mixture of microorganisms and microenvironment) from healthy donors into recipients with dysbiosis, the immunologic pathogenesis by FMT might share characteristics with the pathogenesis by probiotics, although the microenvironment in stool might have an additive effect (96,121-124). For example, dysbiosis induced by antibiotics was rapidly reversed after autologous FMT but not after the administration of probiotics (120). In an animal study, FMT significantly restored $CD4^+$ helper T lymphocyte levels, which had been reduced by antibiotics (74). In a mouse colitis model induced with 2% dextran sulfate sodium (DSS), FMT improved inflammation and helped correct the dysbiosis via augmenting IL-10 production by innate and adaptive immune cells such as $CD4^+$ T cells, invariant natural killer T cells, and Ag-presenting cells. It also decreased major histocompatibility complex II-dependent bacterial Ag presentation to T cells in the colon (158). In a murine model of CDAD, neither B cells nor $CD8^+$ T cells play a critical role in the resolution of CDAD using FMT, but $CD4^+$ T cells do (159). Furthermore, transplantation of gut microbiota from healthy donor mice into mice previously colonized with microbiota from patients with IBD increased $ROR\gamma t^+$ Treg levels while reducing those of Th17 cells (160).

POSTBIOTICS AND MICROBIAL MODULATION

Postbiotics are defined as "preparations of inanimate microorganisms or their components that confer a health benefit on the host," and include metabolites, SCFA, tryptophan metabolites, etc. (161). Postbiotics can also modulate the gut microbiota and systemic metabolic and immune responses. Considering that the cause-and-effect relationship between the microbiome and IBD remains to be clearly elucidated, the idea of targeting metabolites rather than the dysbiosis itself is gaining attention (162). Postbiotics, such as SCFAs or tryptophan, act as messengers that connect the gut microbiota with the innate and adaptive immune systems and do not pose a significant risk to the host, even during

the acute stage of inflammation (163,164). In addition, fermentation products such as organic acids can inhibit pathogens through their anti-inflammatory activity. SCFAs such as acetate, propionate, and butyrate are produced by different pathways in different organisms (40,165). Butyrate is primarily produced by *F. prausnitzii*, *Eubacterium rectale*, *Roseburia intestinalis*, and *Anaerostipes* spp. (40,165). These bacteria provide approximately 70% of the energy required by the colonic epithelium and improve intestinal barrier function and immunity by enhancing antimicrobial defense and mucus production (165). They also maintain intestinal homeostasis and improve epithelial barrier function by activating histone deacetylase and specific G-protein coupled receptors (GPR) such as GPR41 and GPR43 (40,164-166). In addition, SCFAs help regulate electrolytes and are thus involved in energy metabolism and pH regulation in the intestine (165).

MICROBIAL MODULATION BY GENE DELIVERY USING MICROORGANISMS IN IBD

ROS are closely associated with IBD pathogenesis, and a few studies have shown that manipulating ROS metabolism by gene delivery using commensal bacteria can modulate the intestinal microbiota. In addition, atypical mutant *E. coli* with an additional catalase gene was resistant to ROS and showed beneficial effects in DSS-induced colitis by modulating immune responses and microbial composition (167). This study showed that a single gene product of commensal species can modulate the gut microbiota by modifying gut metabolism (168). Recently, recombinant probiotics, particularly those from the genus *Bifidobacterium*, have been developed to produce and secrete IL-10, an anti-inflammatory cytokine, into the intestine more efficiently (169,170).

CONCLUSION

In this review, we have summarized the pathogenesis of gut dysbiosis in IBD. Efforts to modulate gut dysbiosis using various methods, such as antibiotics, probiotics, or FMT, have been attempted with limited success. In summary, antibiotics might be used in limited settings in the management of IBD, although their clinical significance has not been proven. In contrast, probiotics might be beneficial in some patients with UC and pouchitis, with possible synergetic effects if they are administered with prebiotics. In addition, FMT has been shown to have beneficial effects in patients with CDAD. For patients with IBD, FMT may be effective, particularly in UC as opposed to CD. Detailed studies of the changes in microbiota composition and their metabolites by each form of microbial modulation and accompanying clinical improvement will be needed to verify the effectiveness and safety of microbial modulation in clinical studies. In this review, we have also reiterated the need for well-designed studies to evaluate the precise influence of each treatment option for modulating gut dysbiosis in complex microbiota ecosystems. These studies will be necessary to elucidate the relationship between the immune system, gut microbiota, and the intestine in the pathogenesis of IBD.

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