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Update on gut microbiota in gastrointestinal diseases

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Abstract

The human gut is a complex microbial ecosystem comprising approximately 100 trillion microbes collectively known as the “gut microbiota”. At a rough estimate, the human gut microbiome contains almost 3.3 million genes, which are about 150 times more than the total human genes present in the human genome. The vast amount of genetic information produces various enzymes and physiologically active substances. Thus, the gut microbiota contributes to the maintenance of host health; however, when healthy microbial composition is perturbed, a condition termed “dysbiosis”, the altered gut microbiota can trigger the development of various gastrointestinal diseases. The gut microbiota has consequently become an extremely important research area in gastroenterology. It is also expected that the results of research into the gut microbiota will be applied to the prevention and treatment of human gastrointestinal diseases. A randomized controlled trial conducted by a Dutch research group in 2013 showed the positive effect of fecal microbiota transplantation (FMT) on recurrent *Clostridioides difficile* infection (CDI). These findings have led to the development of treatments targeting the gut microbiota, such as probiotics and FMT for inflammatory bowel diseases (IBD) and other diseases. This review focuses on the association of the gut microbiota with human gastrointestinal diseases, including CDI, IBD, and irritable bowel syndrome. We also summarize the therapeutic options for targeting the altered gut microbiota, such as probiotics and FMT.

Key Words: Inflammatory bowel disease; *Clostridioides difficile* (*Clostridium*) infection; Irritable bowel syndrome; Probiotics; Fecal microbiota transplantation

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Core Tip: In this review, we discuss the gut microbiota in human gastrointestinal diseases, including *Clostridioides difficile* infection, inflammatory bowel disease, and irritable bowel syndrome. We review the role of the gut microbiota in human gastrointestinal diseases and the therapeutic options for manipulating it.

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INTRODUCTION

The human gastrointestinal system harbors approximately 100 trillion microorganisms, also known as the gut microbiota, whose collective genetic material comprises at least 100-fold more genetic diversity than the entire human genome[1]. The gut microbiota includes not only bacteria but also archaea, bacteriophages, fungi, and protozoa species. Recent advances in genomic techniques, including next generation sequencing, mediated metagenomics that rely on 16s rRNA gene amplification, and whole-genome sequencing, have helped us to more clearly understand important interactions, such as host-microbiota and microbe-microbe interactions[2]. The recent additions of artificial intelligence and deep learning to the field of research into the gut microbiota have enabled the rapid identification of thousands of microbes[3].

Recent studies have revealed that the gut microbiota is metabolically active and performs various functions, including those associated with nutrition, immune development, and host defense[4]. Therefore, the gut microbiota plays important roles in the maintenance of human health. A perturbation in the composition and function of the gut microbiota is known as dysbiosis[1,4] and accumulated evidence suggests that this condition is involved in the loss of beneficial microbial input or signaling and a colonization of pathogenic microbes. Dysbiosis is thought to trigger inflammatory effects and immune dysregulation associated with human disorders[5-9].

Fecal microbiota transplantation (FMT) is an emerging treatment intended to rebalance the disturbance by introducing feces from healthy donors to diseased individuals. After obtaining intestinal microbiota from an appropriate donor, the samples can be transplanted in a number of ways, including *via* colonoscopy, orogastric tube, enema, or orally in the form of a capsule that contains the freeze-dried substance. FMT has been described in ancient medical literature, and in 4th century China, Ge Hong described the use of human fecal suspension by mouth for patients with severe diarrhea. In modern medicine, FMT was reported in 1958 for pseudomembranous colitis by Eiseman *et al*[10]. In 2013, the first randomized controlled clinical trial of FMT for recurrent *Clostridioides difficile* (*C. difficile*) infection (CDI) was reported[11]. FMT has entered the era of evidence-based medicine, attracting growing interest as a potential treatment for various gastrointestinal diseases, as well as metabolic and cardiovascular diseases.

Probiotics have been defined by an expert group as “live microorganisms, which when administered in adequate amounts, confer a health benefit on the host”[12]. There is an increasing body of evidence indicating that probiotics can be used in the treatment and prevention of infections and chronic inflammatory disorders of the gastrointestinal tract. However, the mechanisms of action of probiotics, which are diverse, heterogeneous, and strain specific, have received little attention. Most studies have mainly reported clinical effects, tolerance, and safety data but have not discussed potential mechanisms of action. Major probiotic mechanisms of action include enhancement of the epithelial barrier, increased adhesion to intestinal mucosa with concomitant inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, production of anti-microorganism substances, and modulation of the immune system[12-14].

In addition to probiotics, other therapeutic interventions for modulating the gut microbiota include prebiotics and synbiotics. Prebiotics have been defined as a substrate that is selectively utilized by host microorganisms conferring a health benefit[15]. Prebiotics compounds stimulate growth, activate metabolism, and promote protection of bacteria that are beneficial to the host organisms. In the intestine, prebiotics selectively enhance the fermentation activity of certain groups of beneficial microbes, such as *Bifidobacterium* and *Lactobacillus* spp.[16]. Prebiotics exert beneficial effects *via* mucin production by providing fermentable compounds that contribute to a prevention of bacterial translocation. The production of metabolites, including folate, vitamins, and short chain fatty acids during their fermentation by gut microbiota shows antimicrobial activity and maintains a healthy gut barrier[12]. Synbiotics are a combination of prebiotics and probiotics that are believed to have a synergistic effect by inhibiting the growth of pathogenic bacteria and enhancing the growth of beneficial organisms[12]. Synbiotics are those products in which the prebiotic compound selectively favors the growth of

probiotics and their metabolite production[15,17]. Synbiotic effects can occur in two ways: by improvement in the host's health after ingestion of a mixture of prebiotics and probiotics strains or by the promotion of indigenous beneficial microbiota, such as *Bifidobacteria* after ingestion of prebiotics alone[15,17]. Multiple mechanisms of prebiotics and synbiotics in controlling growth and infection of enteric bacterial pathogens have been proposed, but systematic studies are still needed to understand how predesign prebiotics and synbiotics can improve the human gut health and prevent diseases (Figure 1).

In this review, we summarize the recent findings regarding the role of the gut microbiota in gastrointestinal diseases, and therapeutic options for targeting it.

CLOSTRIDIODES DIFFICILE INFECTION

C. difficile is a gram-positive, spore-forming anaerobic bacillus that has attracted attention as a cause of antibiotic-associated enteritis. *C. difficile* was first reported to have been found in the feces of healthy newborns in 1935 and was subsequently reported in 1978 as the causative agent of antibiotic-associated pseudomembranous colitis[18,19]. Toxins A and B are important for the onset of CDI. In the United States, around 500000 cases of CDI occur annually, of which about 20% relapse, with approximately 29000 deaths[20]. The increased incidence, severity, and mortality of CDI have been largely attributed to the epidemic strain ribotype 027 (formerly referred to as NAP1/BI/027), which emerged in the early 2000s and has resulted in out-breaks[20]. This strain has high-level fluoroquinolone resistance and can produce substantially higher amounts of toxins A and B than other strains[21,22]. Moreover, it dramatically increases the severity with more incidence of septic shock, toxic megacolon, gut perforation, and death.

Recurrent CDI (rCDI) is usually defined as an episode of CDI occurring within 8 wk of a previous episode. The recurrence rate of CDI also continues to increase, thereby raising important clinical concerns. About 25% of patients who initially respond to antimicrobial therapy experience rCDI. A second recurrence rate of 40% has been reported among patients with resolved first recurrence[20,23]. Advanced age, use of antibiotics, severe underlying disease, chronic kidney disease, proton pump inhibitor exposure, prolonged hospital stays, and previous CDI have been recognized as risk factors[23, 24].

There are two prerequisites for developing *C. difficile* associated diarrhea: disruption of the normal gastrointestinal microbiota, causing diminished colonization resistance favoring *C. difficile*, and acquisition of the organism from an exogenous source[25]. Prolonged antibiotic use is the main risk factor for the development of CDI. Antibiotic therapy causes alterations of the intestinal microbial composition, enabling *C. difficile* colonization and consecutive toxin production leading to disruption of the colonic epithelial cells.

While antibiotics are still the treatment of choice for CDI, a new therapy targeting the gut microbiota called FMT has emerged in recent years[26-28]. FMT is the most direct and effective way of changing the patient's intestinal bacterial composition. FMT is a procedure in which fecal matter, or stool, is collected from a tested donor, mixed with saline or another solution, strained and either placed in a bank or directly into a patient, by colonoscopy, endoscopy, nasogastric tube, or enema[26]. In 2013, a Dutch research group conducted a randomized controlled trial against rCDI and found that FMT was much more effective than antibiotics[11]. Because of these findings, FMT for gastrointestinal diseases has attracted worldwide attention[27,29-33] and several large randomized controlled trials (RCTs) and cohort studies have since been performed, all of which have shown the effectiveness of FMT for rCDI. Moreover, systematic reviews and meta-analyses targeting these studies have been reported[29,34-39]. All reports show the effectiveness of FMT for rCDI, but the methods of FMT vary from study to study. Differences in methodology include those involving donor selection, preparation of fecal material, clinical management, and fecal delivery. Systematic reviews and meta-analyses showed that lower gastrointestinal FMT delivery was more effective than the upper gastrointestinal FMT delivery[34,35]. Moreover, a systematic review showed that encapsulated FMT is as effective as FMT performed through the nonoral route[38,40]. Some systematic reviews and meta-analysis found that there was no difference between frozen FMT and fresh FMT[34,40]. Furthermore, FMT by multiple infusions could effectively and significantly improve the clinical diarrhea remission rate[40]. Collectively, these systematic reviews and meta-analyses indicated the use of FMT *via* colonoscopy or encapsulated FMT, and the use of fresh or frozen feces as being the best strategy for treatment of rCDI.

The American College of Gastroenterology guidelines recommend FMT for severe antibiotic-resistant CDI[41]. The guidelines published by the Infectious Disease Society of America and Society for Healthcare Epidemiology of America consider FMT to be an appropriate treatment for rCDI after standard antibiotic treatment[42].

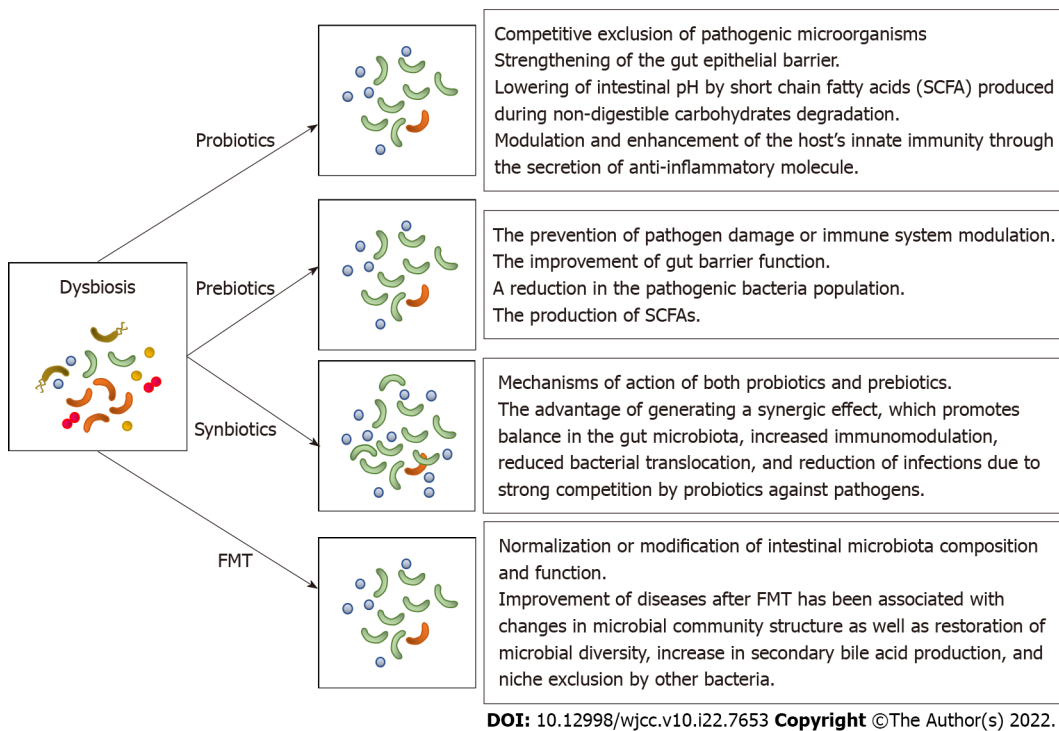


Figure 1 Mechanism underlying the efficacy of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation. Probiotics promote mucin production, production of bacteriocins, and short chain fatty acids (SCFAs), which are responsible for the inhibition of pathogens, inhibition of bacterial translocation, and inhibition of pathogens due to competition for receptors and nutrients. Prebiotics act as nourishment for beneficial bacteria in the commensal microbiota, including the production of SCFAs and antimicrobial peptide. Another mechanism by which prebiotics can inhibit pathogens is by interaction with an adhesion receptor, such as the lectin receptor, demonstrating an antiadhesive action. Synbiotics have mechanisms of action of both probiotics and prebiotics. Moreover, synbiotics have the advantage of generating a synergic effect, which promotes balance in the gut microbiota, increased immunomodulation, reduced bacterial translocation, and reduction of infections due to strong competition by probiotics against pathogens. fecal microbiota transplantation (FMT) provides normalization or modification of intestinal microbiota composition and function. The improvement of human diseases after FMT has been associated with changes in microbial community structure as well as restoration of microbial diversity, increase in secondary bile acid production, and niche exclusion by other bacteria.

FEATURES OF THE GUT MICROBIOTA IN INFLAMMATORY BOWEL DISEASES

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract encompassing two main clinical entities: Crohn's disease (CD) and ulcerative colitis (UC). Although the etiology of IBD remains unknown, it occurs in genetically susceptible individuals after an exaggerated immune response to a normal stimulus, such as food and the gut microbiota[43,44]. Recent studies have suggested that the gut microbiota plays an important role in the pathogenesis of IBD[4].

Many studies have compared the gut microbiota of patients with IBD and healthy individuals. In 2020, Pittayanon *et al*[45] systematically reviewed 48 studies comparing the gut microbiota of IBD patients and healthy individuals. In CD, *Christensenellaceae* (Firmicutes phylum), *Coriobacteriaceae* (Actinobacteria phylum), and *Faecalibacterium prausnitzii* (*F. prausnitzii*) were decreased, while *Actinomyces*, *Veillonella* and *Escherichia coli* (*E. coli*) were increased compared to healthy subjects. It was also reported that *Eubacterium rectale* and *Akkermansia* were decreased, and *E. coli* was increased in UC patients compared with healthy subjects. The diversity of gut microbiota was found to be reduced or not significantly different in IBD patients compared to healthy individuals.

Each study analyzed in the review reported that the gut microbiota of IBD patients and healthy individuals was different. However, it was pointed out that the results of the reviewed studies were inconsistent. One of the most common findings in each of the studies was a decrease in α -diversity compared to healthy individuals and a decrease in *F. prausnitzii* in CD patients and UC patients. *F. prausnitzii* is known as a butyrate-producing bacteria and is thought to contribute to anti-inflammatory properties in CD by inhibiting the NF- κ B pathway in the intestinal epithelium[46]. In addition, *Christensenellaceae*, which has been reported to be reduced in CD patients compared to healthy subjects, belongs to the Firmicutes phylum and is a butyrate-producing bacterium like *F. prausnitzii*[46]. In the Pittayanon *et al*[45] review, it was reported that *Akkermansia* was decreased in UC patients, but it is unclear whether it is the cause or a secondary change due to the pathology of UC patients. Previous studies have reported that *Akkermansia* acts as an anti-inflammatory in colitis, while the energy source of *Akkermansia* is reduced in UC patients, indicating that *Akkermansia* accompanies a decrease in mucus. It is noted that the decrease of *Akkermansia* is a secondary result consequent to the decrease of mucus in UC patients[47]. *E. rectale*, which is also a major butyrate-producing bacterium, is reduced in UC

patients compared to healthy individuals[48]. Collectively, the gut microbiota of IBD patients is characterized by a decrease in butyrate-producing bacteria compared to healthy subjects.

Coriobacteriaceae (Actinobacteria phylum) belong to the same family as *Collinsella*, *Eggerthella*, *Sloackia*, and *Atopobium*. Bile acids have been reported to play an important role in the pathology of IBD, but these bacteria are said to have the ability to convert bile acids, and *Coriobacteriaceae* also have the same function[49]. It is suggested that they may contribute to the pathogenesis of IBD. One of the most common results is an increase in *Escherichia*, especially *E. coli* belonging to the family *Enterobacteriaceae*, which has been suggested to be harmful in IBD. Among *E. coli*, adherent-invasive *E. coli* is known to increase in the ileal mucosa of CD, and inflammation is caused by adhering to and invading the intestinal epithelium[50]. This suggests that an increase in *Escherichia* may be involved in the chronic inflammation of IBD.

As mentioned above, various alterations of the gut microbiota have been reported in patients with IBD. Most studies have demonstrated the reduced diversity of the gut microbiota in IBD patients. However, results related to some bacterial species, such as *Bacteroides*, *Bifidobacteria*, and *E. coli*, vary among studies. These inconsistencies in results may be caused by various factors: (1) The ratio of the number of patients with CD and UC; (2) Disease activity (active or quiescent); (3) Disease activity of sampling location (inflammatory or noninflammatory site); (4) The analysis method of gut microbiota; (5) Medication.

For future studies of the gut microbiota with IBD patients, it is necessary to define which research method is the most appropriate, and to use the same method (including sample storage, DNA extraction, sequencing, and analysis methods) among studies to produce consistent results.

EFFECTS OF PROBIOTICS ON IBD

Probiotics are defined as living microorganisms which, when administered in adequate amounts, confer a health benefit on the host[12]. The concept of probiotics was initially suggested in 1908 by Elie Metchnikoff, a Russian Nobel Laureate who observed that consumption of fermented foods containing lactic acid bacteria had a beneficial effect on human health. Since then, the efficacy of probiotics has been investigated in various diseases and is currently suggested as a possible therapeutic or preventive option in several gastrointestinal diseases[51]. The precise mechanisms of probiotics in human health remain unknown. They have been suggested to act through inhibition of the overgrowth of pathogenic bacteria and the prevention of pathogenic bacterial invasion of the host, and the improvement of gut barrier function by production of substances, such as short chain fatty acids[16].

Some RCTs have been conducted and systematic reviews have analyzed their findings to investigate the efficacy of probiotics on induction of remission and maintenance of remission in IBD patients. The efficacy of probiotics has been examined more extensively in UC than CD but, due to poor study design or the small number of subjects, their efficacy on IBD currently remains unknown.

A systematic review of 14 RCTs examined the efficacy of probiotics on induction of remission in active UC patients. The review showed that the induction of remission rate was higher in the probiotic group than the placebo group (RR: 1.73, 95%CI: 1.19-2.54). In contrast, the induction of remission rates were similar in the placebo group and the 5-aminosalicylic acid (ASA) group (RR: 0.92, 95%CI: 0.42-2.59)[52]. Moreover, another systematic review of 12 RCTs investigated the efficacy of probiotics on maintenance of remission in UC patients. It showed that no clear superiority was observed in the maintenance of remission rate in the probiotic group compared to the placebo group (RR: 0.87, 95%CI: 0.63-1.18) or the 5-ASA group (RR: 1.01, 95%CI: 0.84-1.22)[53].

A systematic review of two RCTs reported on the efficacy of induction of remission in CD patients. The review showed that the induction of remission rate in the probiotic group was higher than the placebo group at 6 mo after administration (RR: 1.06, 95%CI: 0.65-1.71)[54]. However, another systematic review did not point out the efficacy of probiotics on the maintenance of remission in CD patients[55]. Regarding adverse events associated with probiotics, no significant difference was shown between the probiotic group and the placebo group.

It will be necessary to conduct large-scale RCTs with many subjects in the future to establish high-quality evidence on the efficacy of probiotics on the induction and maintenance of remission in IBD patients. Moreover, further research is warranted to elucidate the underlying biological mechanisms.

THE EFFICACY OF FECAL MICROBIOTA TRANSPLANTATION ON IBD

The effect of FMT has been investigated as a therapeutic option targeting the gut microbiota of IBD.

A 2018 Cochrane's systematic review analyzed the efficacy of FMT on UC[56]. The remission rates at week 8 were 37% (52/140) and 18% (24/137) in the FMT group and the control group, respectively (RR 2.03, 95%CI: 1.07-3.86). Forty-nine per cent (68/140) of FMT participants had a clinical response compared to 28% (38/137) of control participants (RR 1.70, 95%CI: 0.98-2.95). Thirty percent (35/117) of FMT participants achieved endoscopic remission compared to 10% (11/112) of control participants (RR

2.96, 95%CI: 1.60-5.48). The relapse rate at 12 wk after FMT was 0% and 20% in the FMT group and the control group, respectively (RR 0.28, 95%CI: 0.02-4.98). Furthermore, regarding serious adverse events, no significant difference was observed between the FMT group (7%, 10/140) and the control group (5%, 7/137) (RR 1.40, 95%CI: 0.55-3.58). On the other hand, RCTs have not investigated the efficacy of FMT on the induction of remission in CD patients.

A meta-analysis of seven RCTs, including 431 subjects, evaluated the efficacy of FMT on UC[57]. The clinical remission rates were 47.9% and 31.3% in the FMT group and the placebo group, respectively. Sub-analyses were performed on the method of administration, donor selection, and fresh or frozen feces, and showed that to administer frozen feces collected from multiple donors to the lower gastrointestinal tract was highly effective. A systematic review of 6 RCTs and 24 cohort studies examined the efficacy of FMT on IBD[58]. The review showed that FMT achieved a clinical remission rate of 37.0%, a clinical efficacy rate of 53.8%, and adverse events of 29.2%.

Currently, FMT is not recommended as a therapeutic option for IBD in clinical practice guidelines. In Japan, FMT is not recommended as a treatment option for IBD in the clinical practice guidelines. According to the guidelines of the European Crohn's and Colitis Organization[59,60], American Gastroenterological Association (AGA)[61,62], ACG[63,64], and British Society of Gastroenterology[65], FMT is not mentioned as a treatment option for IBD. In each of the clinical guidelines, high-quality RCTs should be conducted in the future to define the method and frequency of administration, dosage of feces, pretreatment method, donor selection criteria, and disease activity so that the long-term efficacy of FMT can be ascertained.

CHARACTERISTICS OF THE GUT MICROBIOTA IN IRRITABLE BOWEL DISEASE

Irritable bowel disease (IBS) is a typical functional gastrointestinal tract disease, estimated to affect around 11.2% of the world's population[66]. The clinical features of IBS include bloating, flatulence, abdominal pain, or discomfort associated with a change in bowel habits, such as diarrhea, constipation, or a mix of the two. The pathophysiology of IBS remains unknown, but it is suggested that the condition is multifactorial, affected by genomes, cerebrointestinal peptides, gastrointestinal motility abnormalities, visceral hypersensitivity, gastrointestinal immunity, mucosal permeability, the gut microbiota, and psychosocial factors. This relationship between the brain and gastrointestinal function is called the gut-brain axis, which is an important concept when considering the pathophysiology of IBS. Although in recent years, accumulating evidence has suggested that the alternation in the gut microbiota plays an important role in the pathophysiology of IBS, a concept has arisen from clinical observations of symptoms developing after an infection, also known as post-infectious IBS[67].

There have been numerous comparative studies of the gut microbiota of IBS patients and healthy individuals. In 2019, Pittayanon *et al*[68] systematically reviewed 24 studies comparing the gut microbiota of IBS patients with healthy individuals. Four studies showed that the Proteobacteria is increased in IBS patients compared to healthy individuals at the phylum level, while another two reports showed that there was no significant difference of the gut microbiota between IBS patients and healthy individuals. Consistent results were not obtained for Bacteroidetes, Actinobacteria, or Firmicutes. In addition, an analysis at a lower-level than the phylum reported a significant increase in *Enterobacteriaceae* (Proteobacteria) and *Bacteroides* (Bacteroidetes) in IBS patients compared to healthy individuals. However, another two studies showed that there was no significant difference in these bacteria between the two groups.

Pathogenic bacteria, such as *Escherichia*, *Shigella*, *Campylobacter* and *Salmonella* belong to the family *Enterobacteriaceae*. In addition, approximately 10% of IBS patients believe that their symptoms began following a bout of infectious dysentery, leading to the coinage of the term post-infectious-IBS, and it is presumed that dysbiosis occurring as a result of infection causes IBS-like pathology. Post-infectious IBS may be associated with these pathogenic bacteria. The genus *Bacteroides* also contains bacteria that produce intestinal toxins, such as *Bacteroides fragilis*, which breaks down glycoproteins in mucus[69] and affects the wall movement (motility), which induces symptoms of IBS, including abdominal pain and diarrhea[70].

Three studies from Europe reported a reduction of Clostridiales I, difficult-to culture bacteria, in IBS patients, which is the most consistent result. In addition, four other studies showed a significant reduction in *Faecalibacterium* (Clostridiales) in 119 patients with diarrhea-predominant IBS. Furthermore, two studies showed a significant reduction of *F. prausnitzii* in the IBS group compared to healthy individuals, while two other studies showed a non-significant reduction of *F. prausnitzii* in the IBS group compared to the control group. It has been suggested that these bacteria, including Clostridiales I and *F. prausnitzii*, may play a protective role in IBS.

F. prausnitzii, which belongs to the order Clostridiales, is known to contribute to the maintenance of homeostasis of the intestinal tract. *F. prausnitzii* is known to be a bacterium that exerts an anti-inflammatory effect by having the ability to produce butyrate. It has been reported that in a rat model, *F. prausnitzii* regulates the production of interleukin-17, leading to the improvement of IBS symptoms[71]. The genus *Bifidobacterium* (Bifidobacteriaceae) was examined in seven studies, five of which reported a

significant decrease in the genus *Bifidobacterium* in IBS patients, but another of which reported a tendency to decrease but no significant difference in *Bifidobacterium* in IBS patients. The genus *Tannerella* (Phylum Bacteroidetes) was reported to be significantly reduced in two studies, while no significant difference was noted in the other two studies. The genus *Bifidobacterium* is reduced regardless of the subtype of IBS, suggesting that *Bifidobacterium* may improve IBS symptoms. A placebo-controlled trial of *Bifidobacterium longum* for IBS found that the *Bifidobacterium longum* group had improved depression scores and QOL of IBS patients compared to a placebo group. It has been suggested that p-cresol sulfate is decreased in the *Bifidobacterium longum* group, which may contribute to IBS symptoms[72]. p-Cresol sulfate has been shown to reduce the oxygen consumption of colonocytes and to be cytotoxic[73]. The production of p-cresol sulfate is dependent upon intestinal environmental factors, such as the composition of the microbiota, food intake, and pH of the intestinal tract[74]. p-Cresol sulfate is synthesized from tyrosine and phenylalanine *via* 4-hydroxyphenylacetate by the gut microbiota. *Clostridioides difficile* and certain *Lactobacillus* strains are known to produce p-cresol by decarboxylation of 4-hydroxyphenylacetate[75,76]. Furthermore, bacterial production of bioactive substances from dietary protein has been implicated in inflammation and tissue permeability in the gut[77]. Moreover, p-cresol sulfate has been shown to act on the dopamine / norepinephrine pathway in depressive symptoms[72]. In addition, a systematic review of probiotics for IBS reported that the IBS symptoms were improved in the group containing *Bifidobacterium* compared to the control group.

The diversity of the gut microbiota of IBS patients has been investigated. Nine studies examined α -diversity in IBS patients and, of these, five reported that α -diversity in the gut microbiota was significantly reduced in IBS patients compared to healthy individuals while the other four reported no significant difference.

In subgroup analysis, gut microbiota has been analyzed according to IBS subtype, including diarrhea-predominant IBS (IBS-D), constipation-dominant IBS (IBS-C), and mixed bowel habit IBS subtype (IBS-M)[68]. Six studies described the gut microbiota in 130 subjects with IBS-M and all found no differences between this subtype and IBS-C or IBS-D. In all cases, any differences between IBS and healthy control were the same in the IBS-M group compared with the IBS-C or IBS-D subgroups. In terms of IBS-D, 3 of 5 articles assessing genus *Bacteroides* demonstrated a significant increase of this genus in IBS-D patients, whereas another 2 showed insignificant results compared to controls. In contrast, the majority of studies evaluating the genus *Bifidobacterium* showed a significant decrease in IBS-D patients. Only one study evaluated IBS-C alone. This study found differences between IBS-C and healthy controls, but it is difficult to draw conclusions from one study.

As in the studies of the gut microbiota of IBD, the conclusions of the studies of the gut microbiota in IBS also lacked consistency. It is considered that the inconsistency of results was mainly caused by the variety of research methods.

THE TREATMENT FOR IBS TARGETING THE GUT MICROBIOTA

Several therapeutic options aimed at improving dysbiosis in IBS patients, including probiotics and FMT, have been studied. Probiotics supplements with beneficial effects on IBS symptoms may lead to more effective therapeutic options. The proposed theory is that the supplementation of probiotics improves IBS symptoms by modulating or restoring the gut microbiota or its metabolic pathways[78]. A meta-analysis published in 2018 comprehensively analyzed thirty-seven studies (21 combinations of probiotics, total of 4430 subjects), which examined the efficacy of probiotics on IBS[79]. It was shown that probiotics were effective in improving IBS symptoms. This meta-analysis has demonstrated that amongst combination probiotics, LacClean Gold, which consists of *Bifidobacterium longum* (*B. longum*), *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus* (*L. acidophilus*), *Lactobacillus rhamnosus*, and *Streptococcus thermophilus* and the seven-strain combination of three *Bifidobacterium*, three *Lactobacillus* and one *Streptococcus* were associated with significant improvement in IBS global symptoms, and there was a trend towards an improvement in global symptom scores or abdominal pain scores with LSL#3, a probiotic mixed with 4 *Lactobacilli* (*L.*) (*L. casei*, *L. acidophilus*, *L. delbrueckii* subsp., *Bulgaricus*), 3 *Bifidobacteria* (*B.*) (*B. longum*, *B. breve*, *B. infantis*), and a *Streptococcus* (*Streptococcus-salivarius* subsp. *thermophilus*). However, this study has shown a limitation that for probiotics, it remains whether a particular combination of probiotics, or a specific species or strain, is more likely to be effective, or there is a particular IBS subtype that is more likely to benefit. A therapeutic option for IBS using probiotics is expected to become more important in the future.

A systematic review published in 2019 comprehensively analyzed four RCTs that examined the effects of FMT on IBS patients[80]. One study included IBS-D only, 2 studies included IBS without constipation, and 1 study included all 3 subtypes of IBS. It showed that the response rates were 49.3% and 51% in the FMT group and the placebo group, respectively, suggesting FMT is not effective for IBS symptoms. This study did not show the subgroup analysis according to IBS subtypes. However, FMT for IBS is not recommended in clinical practice guidelines of IBS. The clinical guidelines of IBS provided by the Japanese Society of Gastroenterology, ACG[81], AGA[82], and the British Society of Gastroenterology[83] do not recommend the use of FMT due to insufficient evidence of its efficacy for IBS in

clinical studies, and point out the need for large-scale and high-quality RCTs in the future.

ADVERSE EVENTS OF FMT

A systematic review analyzing FMT-related adverse events has been reported[84]. It analyzed 129 studies, including 4241 subjects and a total of 5688 FMTs. The incidence rate of adverse events was 19.0%. Most reported adverse events were self-limiting gastrointestinal symptoms comprising abdominal discomfort/abdominal pain/abdominal bloating (7.0%) and diarrhea (10%). Serious adverse effects such as infection and death were reported in 1.4% of patients. Although current evidence deems FMT to be a generally safe therapeutic method with few adverse events, the long-term outcomes of its use have not been completely elucidated. Therefore, establishing periodicity and length of regular follow-up after FMT to monitor the clinical efficacy and long-term adverse events are other essential issues. Aside from standardization of donor screening and clear protocols for adverse events monitoring, an FMT registry should be established to collect long-term data and follow-up outcomes and complications.

CONCLUSION

In the present review, we provided an overview of the role of the gut microbiota in the pathogenesis of CDI, IBD, and IBS and of promising treatments aimed at the modulation of the gut microbiota, including FMT and probiotics.

Microbiome research has been able to reap the benefits of technological advancements in systems and synthetic biology, biomaterials engineering, and traditional microbiology. Recently, gut microbiome research has been revolutionized by high-throughput sequencing technology, permitting composition and functional analyses. The accumulating evidence by using sequencing technology enables us to understand the role of the gut microbiota in human diseases.

FMT is considered effective in restoring imbalances of the gut microbiota. Consequently, it can be performed in a variety of human diseases associated with dysbiosis, including not only gastrointestinal diseases, but other systemic disorders such as metabolic syndrome, diabetes mellitus, autoimmune diseases, and cardiovascular diseases. Many unanswered questions remain however, including identification of a standardized FMT methodology for factors, such as the optimal route of administration and donor selection, as well as those concerning the long-term benefits of FMT and adverse effects.

Probiotics have considerable potential for preventive and therapeutic applications in various gastrointestinal disorders. Although, from the ongoing research more promising potential health effects of probiotics are being observed, more standardized and verifiable clinical studies are needed to demonstrate the safety, efficacy, and limitations of a putative probiotic, to determine whether it is superior to existing therapies, and to determine both the short- and long-term effects on the immune system in healthy and diseased individuals.

FOOTNOTES

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