



Therapeutic Modulation of Gut Microbiota in Functional Bowel Disorders

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Functional bowel disorders (FBDs) are functional gastrointestinal disorders with symptoms attributable to the middle or lower gastrointestinal tract. These include irritable bowel syndrome, functional bloating, functional constipation, functional diarrhea, and unspecified FBD. Increasing evidence has emerged of late that intestinal microbiota is involved in the pathogenesis of FBDs. In this review, the therapeutic benefits and future perspectives of the currently available strategies for modifying the gut microbiota in FBDs are described, focusing primarily on irritable bowel syndrome and functional constipation.

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Key Words

Diet; Fecal microbiota transplantation; Irritable bowel syndrome; Microbiota; Probiotics

Introduction

Functional bowel disorders (FBDs) are functional gastrointestinal disorders with symptoms attributable to the middle or lower gastrointestinal tract.¹ These include irritable bowel syndrome (IBS), functional bloating, functional constipation (FC), functional

diarrhea, and unspecified FBD.¹ The FBDs are among the most common gastrointestinal complaints, and they are associated with reduced quality of life.^{2,3} The pathophysiological mechanisms underlying these disorders are still incompletely understood, but they may be multifactorial, including visceral hypersensitivity, abnormal gastrointestinal motility, altered brain-gut axis, psychological disturbances, and low-grade inflammation.^{4,5} Increasing evidence has

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emerged of late that intestinal microbiota is involved in the pathogenesis of FBDs.⁶

The phenomenon of post-infectious IBS, small-intestinal bacterial overgrowth implicated in the subgroups of IBS, and alteration of the fecal microbiota of IBS patients directly support the importance of gut microbiota in IBS pathophysiology.⁶⁻¹² The known physiologic effects of altered microbiota include bile salt deconjugation changes leading to changes in stool volume and consistency, as well as bacterial fermentation changes resulting in alterations in the gas volume and/or composition. These alterations indirectly support the role of gut microbiota in the development of FBDs.⁸

The treatment of FBDs remains challenging. An improved understanding of host-microbiota interactions in FBDs is important not only for its pathogenesis but also for enabling therapeutic modulation of the microbiota.¹³ The potential therapeutic approaches, including dietary manipulation, prebiotics, probiotics, synbiotics, antibiotics, and fecal microbiota transplantation, are attempts to modify the gut microbiota.⁶ In this review, the therapeutic benefits and future perspectives of the currently available strategies for modifying gut microbiota in FBDs are described, focusing primarily on IBS and FC.

Diet and Intestinal Microbiota

As the knowledge about the human gut microbiome has advanced, the composition of the microbiota has been discovered to have a profound impact on human health.^{14,15} The human gut microbiota is influenced by various factors. Of these, diet is a key element determining its composition.^{15,16} Carbohydrate fermentation is a core activity of the human gut microbiota, driving the energy and carbon economy of the colon.^{17,18} Short-chain fatty acids (SCFAs), which are the main end products of bacterial metabolism, regulate the intestinal physiology and immune function, and act as a substrate for lipogenesis and gluconeogenesis.¹⁷ Therefore, it is recognized that certain foods may affect the microbiota activities linked to the systemic host physiology.

For IBS patients, food is an important issue in the management of their symptoms. A large number of IBS patients consider their symptoms related to food, and two-thirds of IBS patients report restricting their diets.¹⁹⁻²³ Many different dietary approaches for the management of the IBS symptoms have been tried over the years.²⁴ There are many mechanisms by which food may act on the gut to cause symptoms of IBS.^{23,25} Among these, altered microbial composition and functions of food may be important factors in the development of IBS symptoms. Thus, therapeutic dietary interven-

tions that modify gut microbiota may be effective for alleviating IBS symptoms. In this section, the evidence for a link among diet, gut microbiota, and IBS symptoms are reviewed.

There is emerging strong evidence supporting diets for the IBS patients that are low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). Randomized controlled trials (RCTs) reported that a diet low in FODMAPs effectively reduced IBS symptoms, and the effects were comparable with those of the traditional IBS dietary advice.^{26,27} FODMAPs exacerbate IBS symptoms through various mechanisms, such as by increasing the small-intestinal water volume through an osmotic effect, colonic-gas production by bacterial fermentation, and altered intestinal motility.²⁸ Carbohydrates fermented by the gut microbiota cause increased production of luminal gases, such as hydrogen, methane, and carbon dioxide.²⁹ Excess hydrogen leads to luminal distension, resulting in increased bloating and borborygmi in those with visceral hypersensitivity.³⁰ An unblinded study found that when challenged with a high-fermentable-carbohydrate “flatulogenic” diet, the frequency and volume of flatulence and other gastrointestinal symptoms increased compared with the baseline in both flatulence patients and the healthy controls.³¹ Moreover, flatulogenic diet revealed instability of the microbial composition and reduction of the microbial diversity in patients complaining of flatulence, whereas healthy controls’ microbiota were stable. This study indirectly demonstrated the impact of the diet-microbiota interactions on the development of symptoms in IBS patients.

Methanogenic archaea, a major mechanism of hydrogen disposal in the human colon, may also contribute to the pathology of IBS.³² In previous studies, IBS patients had lower numbers of methanogenic bacteria compared with healthy controls, suggesting that IBS patients lack the functions for hydrogen removal.^{11,33} Methane also induces slow intestinal transit, and has been associated with constipation-dominant IBS (IBS-C).³⁴ A study with 19 IBS-C patients found that *Methanobrevibacter smithii* is the predominant methanogen, and that the quantity of *M. smithii* in the stool correlated with the amount of methane excreted in the breath.³⁵ The direct evidence for the role of methane in the diet-microbial interaction in IBS patients, however, is limited; thus, additional studies are warranted.

SCFAs are the main products of FODMAP fermentation, but the alteration or effect of SCFAs in IBS remains unknown. One case control study reported that IBS patients had higher levels of acetic acid and propionic acid than controls, and that the levels of acetic acid and propionic acid were associated with IBS symptom severity.³⁶ It is not clear, however, if this alteration of the SCFAs was

the simple result of the diet or the causal factor of IBS symptoms; therefore, further evaluation of the causal links among the FODMAPs, SCFAs, gut microbiota, and IBS symptoms is needed.

Although many clinical studies have demonstrated the effect of a low-FODMAP diet on symptoms of IBS, the impact of low-FODMAP intervention on the gut microbiota and its association with IBS symptoms have not been well evaluated. Two studies have investigated the impact of low-FODMAP diet on the gut microbiota in adult patients.^{37,38} The first randomized controlled study, with 41 IBS patients, found that more patients in the intervention group (low-FODMAP-diet group) reported adequate symptom alleviation compared with controls (habitual-diet group). Also, IBS patients had lower concentrations and proportions of *Bifidobacterium* than controls.³⁷ A randomized crossover study with 27 IBS patients and 6 healthy subjects found that low-FODMAP diet reduced the total bacterial abundance, and the typical Australian diet increased the relative abundance of butyrate-producing *Clostridium* cluster XIVa and mucus-associated *Akkermansia muciniphila* bacterial groups that may have some health benefits.³⁸ These studies showed the contradictory responses of gut microbiota and IBS symptoms to low-FODMAP diet. Further studies are warranted to elucidate the role of altered microbiota through the restriction of FODMAPs in the alleviation of IBS symptoms and its long-term effect on the general health of IBS patients.

Dietary fat may play a role in the pathogenesis of IBS.³⁹ A substantial number of people with IBS report that their symptoms are associated with fatty food, and that they frequently avoid fatty foods to alleviate the symptoms.^{19,21,39,40} In people with IBS, the lipid-induced inhibition of gut-propulsive motility is up-regulated, and the colonic hypersensitivity in response to the duodenal lipid infusion is exacerbated.^{39,41,42} These effects may be associated with various IBS symptoms. The altered composition of the intestinal microbiota by dietary fat may also be responsible for IBS symptoms. In IBS patients, there is a strong mucosal immune activation predominantly characterized by activated T lymphocytes and mast cells, along with evidence of an increased release of mediators known to signal to epithelial, neuronal, and muscle cells, leading to intestinal dysfunction. The immune activation in low-grade inflammation may be the consequence of the perturbation of gut microbiota.⁴³ A high-fat diet alters the composition of the intestinal microbiota, and this promotes intestinal inflammation.⁴⁴⁻⁴⁷ In one study, a high-fat diet induced increasing ileal tumor necrosis factor alpha mRNA only in conventionally raised, specific-pathogen-free mice and not in germ-free mice.⁴⁶ It changes the behavior as well as the composition of the intestinal microbiota in genetically susceptible hosts, and promotes

inflammation.⁴⁷

Dietary fat also increases the excretion of bile acids. The intestinal microbiota involved in bile acid metabolism, and increased colonic bile acid exposure, may induce IBS symptoms by stimulating colonic motility and secretion, and modulating the microbial composition.^{48,49} A significant increase in fecal primary bile acid and dysbiosis in the feces involved in bile acid transformation were noted in people with diarrhea-dominant IBS (IBS-D).⁴⁸ A diet high in saturated-milk-derived fatty acids increased the formation of taurine-conjugated bile acids in genetically susceptible *III10^{-/-}* mice, promoting the expansion of a low-abundance, sulphite-reducing pathobiont, *Bilophila wadsworthia*, leading to colitis.⁵⁰ There have been no well designed studies, however, that have investigated the effect of the altered gut microbiota on IBS symptoms by restricting dietary-fat intake.

Dietary proteins are also related to IBS symptoms. An example is gluten, which is regarded as a major issue in IBS. Recent studies found that a large number of IBS patients suffer from non-celiac gluten sensitivity.⁵¹ Gluten causes IBS symptoms in people with IBS, and a gluten-free diet reduces IBS symptoms in people with IBS-D.^{52,53} Gluten generates IBS symptoms through altered gut permeability, tight-junctional biology, and enhanced systemic immune responses.⁵³ There is no evidence, however, of the impact of gluten intake on intestinal microbiota, and of its association with IBS symptoms.

Targeting the diet and microbiota remains an attractive option in treating or preventing FBDs. In the future, engineered diets that restrict deleterious components but supplement beneficial nutrients can be used to modify the luminal intestinal environment for the treatment or prevention of diseases.⁵⁴ Human dietary-intervention studies in FBDs are scarce, however, because a dietary-intervention study has many limitations, such as the inability to use placebos as controls and the difficulty of accurately capturing the dietary intake. Many clinical studies on diets have been limited to specific nutrients and foods, but the interactions between the foods consumed, the proportion of food intake, and the effect of the food structure and/or cooking practices should also be considered.¹⁶

The development of therapeutic dietary strategies for modifying the gut microbiota for FBDs is still in the beginning stage. More fundamental studies on the effect of diet on gut microbiome and the pathogenesis of FBDs are needed. A common agreement is also needed on what constitutes a healthy population of gut microbes, and inter-individual differences in the populations of gut microbiota should be considered.^{15,16} Further studies to elucidate the interplay of diet, microbiota, genetic factors, the host immune system, and the

symptoms of FBD are also warranted. The compositional change of the gut microbiota, as well as the gene expression profiles and functionality, should be proven. An investigation of the role of gut microbiomes as biomarkers for dietary intake, disease development, and/or treatment response would be interesting.

Pre- and Probiotics in Functional Bowel Disorders

Lactobacillus and *Bifidobacterium* are the representative components of commercialized probiotic products. There are plenty of literatures that assess the efficacy and safety of these 2 probiotic genera. On the other hand, there are still few literatures that assess other genres, such as probiotics *Escherichia* or *Saccharomyces*. Combination products containing 2 or more probiotic species have become the mainstream of late. “Strain specificity” means that a species of probiotics can have a different level of anti-inflammatory property or resistance to gastric acid or bile salt.⁵⁵ It is reasonable that a probiotic species can show a wide spectrum of efficacy levels in IBS patients according to the source that determines the strain as a subtype of the species. The proven efficacy of one strain of a species cannot be extrapolated to other strains of the species. In the same context, the “non-efficacy of a strain of a species” does not mean that the other strains of the species cannot be effective. A probiotic strain that has been proven to be effective through RCTs may not be available in a certain country at a specific time. Moreover, probiotic products are classified not as drugs but as food items in most countries. In this case, the efficacy data is not obligatory for marketing approval. Clinicians should be aware of the scientific evidence before using probiotic products. There may be no clinical data, however, about a specific strain or a combination product. A clinical decision based on the comprehensive knowledge about the efficacy of probiotics can be essential.

Global Efficacy of Probiotics in Irritable Bowel Syndrome: Dichotomous Assessment by Patients

A dichotomous question about the global efficacy or persistence of symptoms may be difficult to answer for patients, and may be substantially influenced by recall bias, but it seems to be a good indicator of patient satisfaction. Ford et al⁵⁶ performed a comprehensive meta-analysis of 23 placebo-controlled RCTs with IBS patients and reported that the relative risk of IBS symptoms persisting or remaining unalleviated after treatment with probiotics vs placebo

was 0.79 (95% CI, 0.70-0.89). Although a significant effect was observed, a statistically significant heterogeneity was detected among the studies, which may be partially due to the different proportions of IBS subtypes. The consensus agreement and the grade of the evidence for the effect of the probiotics were lower in IBS-C than in IBS-D.⁵⁷

Abdominal Pain and Discomfort: Global Irritable Bowel Syndrome or Abdominal-pain Scores

A meta-analysis of 24 RCTs presenting the global IBS or abdominal-pain scores reported a significant symptom alleviation through a pooled analysis with 2001 patients.⁵⁶ No significant effect was observed, however, in the per-strain or per-product analyses of 2 to 3 RCTs, respectively: *L. plantarum* DSM 9843^{58,59}; *B. infantis* 35624^{60,61}; VSL #3⁶²⁻⁶⁴; a combination product of *L. paracasei sub-species paracasei* F19, *L. acidophilus* La5, and *B. lactis* Bb12⁶⁵⁻⁶⁷; and the other combination of *B. lactis* DN-173 010, *S. thermophilus*, and *L. bulgaricus*.^{68,69}

A systematic review of 18 RCTs involving 1806 IBS patients and consensus voting reported a high grade of evidence for the effect of probiotics on abdominal pain, and a good consensus agreement.⁵⁷ The abdominal pain was significantly alleviated in 5 of the 6 RCTs in which abdominal pain was assessed as a primary outcome variable, but in only 3 of the 12 RCTs in which abdominal pain was evaluated as a secondary variable.⁵⁷ Unexpectedly, the *Lactobacillus plantarum* MF 1298 strain, which had been known to increase the expression of the tight-junction protein through an in vitro study, was reported to aggravate the symptoms, including abdominal pain, discomfort, urgency, and diarrhea, after 3-week treatment in 16 IBS patients.⁷⁰

Bloating and Flatulence

A meta-analysis of 17 separate RCTs involving 1446 patients showed a significant effect of probiotics on the bloating scores.⁵⁶ An international guide through a systematic review and consensus voting reported 70% agreement and a moderate grade of evidence for the effect of certain probiotics on bloating in people with IBS.⁵⁷

There were 10 RCTs involving 741 patients who reported a significant effect of probiotics on their flatulence scores. An RCT reported the effect of *Lactobacillus reuteri* on the passing of gases in 54 patients after 6-month administration. There was no significant effect on the abdominal-pain or sum scores. The flatulence scores

decreased consistently, however, for 6 months in the treatment group compared to the placebo.⁷¹ Although the above-mentioned study showed negative results, it may be an example of a study that showed a promising probiotic strain that could effectively alleviate a specific symptom of IBS.

Urgency, Bowel Habit, Borborygmi, and Feeling of Incomplete Evacuation

Six RCTs reported no significant benefit of probiotics on the urgency scores.⁵⁶ There is a still controversy about the effect of probiotics on the bowel habits, including the stool consistency and the frequency of defecation. Of the 2 RCTs in which the bowel habits were assessed as the primary outcome variable, Kim et al⁶² evaluated the IBS symptoms and gastrointestinal transit times in 25 IBS-D patients before and after the treatment with VSL#3 for 8 weeks. Although the bloating was significantly alleviated, there was no additional effect over placebo on the frequency of bowel movement, stool consistency, gastric emptying time, and colonic transit time. In a study about 6-month treatment with a probiotic mixture containing *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, *Bifidobacterium breve* Bb99, and *Propionibacterium freudenreichii* spp. *shermanii* JS in 103 IBS patients, there were significant effects on the global abdominal symptoms, borborygmi, bowel urgency, and feeling of incomplete evacuation, but there was no change in the bowel habits.⁷² Six of the 14 RCTs in which the bowel habits were assessed as a secondary outcome variable revealed no changes in the bowel frequency and stool consistency.⁵⁷ The above-mentioned RCT with the *L. plantarum* MF 1298 strain showed a significant deterioration of diarrhea and urgency in IBS-D.⁷⁰

Colonic Transit Time and Constipation

There were several RCTs that evaluated the effect of probiotics on the colonic transit time in constipation. In 36 healthy females, the whole and sigmoid colonic transit time significantly decreased after the ingestion of a fermented milk product containing the *Bifidobacterium lactis* DN-173 101 strain 3 times a day for 10 days.⁷³ There was a significant decrease in the whole and right-side colonic transit time as well as an improvement in the abdominal-pain and bowel urgency scores after the ingestion of a fermented milk product containing the *B. lactis* DN-173 010 strain twice a day for 4 weeks in 34 IBS-C patients, but there was no change in the defecation frequency, stool consistency, and defecation discomfort such as straining or feeling of incomplete evacuation.⁶⁸ Krammer et al⁷⁴

reported that the colonic transit time and the subjective symptoms of constipation improved after the treatment with a yoghurt containing *Lactobacillus casei* Shirota once a day for 4 weeks in 24 people with slow-transit constipation. The ingestion of a yoghurt combined with capsules containing *B. lactis* HN019 decreased the whole gut transit time in a dose-dependent manner, and reduced the frequency of the functional gastrointestinal symptoms, in 88 healthy volunteers with gastrointestinal symptoms.⁷⁵ There are several limitations, however: the 3 RCTs evaluated only the short-term effect of fermented milk products and could not demonstrate the effect on the bowel habits, and the Rome III criteria for FC were not applied before the subject selection.

Four RCTs evaluating probiotics in 160 patients who had met the Rome criteria for FC were identified.⁷⁶⁻⁷⁹ An RCT on a fermented milk product containing *L. casei* Shirota did not show any improvement in the bowel habits or alleviation of the subjective symptoms of constipation.⁷⁷ Two of the 4 RCTs showed an increase in the number of bowel movements after the treatment with probiotics, but there was no effect on the stool consistency, straining, and feeling of incomplete evacuation.^{76,78} Riezzo et al⁷⁹ reported that a probiotic-enriched artichoke containing *Lactobacillus paracasei* IMPC 2.1 significantly improved the hard-stool, bowel movement frequency, and feeling-of-incomplete-evacuation scores compared with the control artichoke. Artichoke is a vegetable that is rich in inulin-type fructan, which is one of the representative prebiotics. Apart from improvements in the bowel habits and alleviation of the subjective symptoms of constipation, this study on synbiotics also revealed a significant increase in the concentration of fecal propionic acid, which is a kind of SCFA.⁷⁹ These results warrant future studies about the ideal symbiotic combinations as both safe and sustainable treatment options for constipation.

Safety of Probiotics in Gastrointestinal Disorders

Although probiotics have an excellent overall safety record, they should be used with caution in certain patient groups, particularly in neonates born prematurely or with immune deficiency.⁸⁰ Fears that live probiotic organisms may lead to systemic sepsis have been allayed by the absence of such reports from studies among people with inflammatory bowel disease (IBD) where the intestinal barrier may be compromised. Two notes of caution must be mentioned herein.⁸¹ The first relates to reports of septicemia occurring among infants with short bowel syndrome,⁸² and the second concerns instances of increased mortality among people with severe acute

pancreatitis who had been administered a probiotic cocktail through a nasogastric tube. These deaths were associated not with sepsis but with intestinal ischemia, whose etiology remains unclear.⁸³

Fermented Milk: Probiotics vs Synbiotics vs High-FODMAP Foods

Prebiotics are defined as non-digestible but fermentable foods that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon. The oligosaccharide in human breast milk is considered the prototypic prebiotic as it facilitates the preferential growth of *Bifidobacterium* and *Lactobacilli* in the colons of breastfed neonates.⁸¹ To some degree, a fermented milk product is required to contain lactose, which is a poorly digestible disaccharide in most adults. Moreover, fructo-oligosaccharide is often added to the bacterial yoghurts in the market, as a functional ingredient. It seems reasonable to regard commercialized bacterial yoghurts as synbiotics rather than probiotics. Since recently, a diet low in FODMAPs has often been used to manage the functional gastrointestinal symptoms in IBS patients.⁸⁴ Fermented milk products, which are high in lactose or oligosaccharides, may be a major source of FODMAPs and are likely to aggravate the functional gastrointestinal symptoms in some people with IBS.

Antibiotics in Functional Bowel Disorders

There have been various attempts to treat intestinal symptoms by using various antibiotics.⁸⁵⁻⁸⁷ Finally, in 2015, rifaximin became the first Food and Drug Administration-approved antibiotic for the treatment of IBS-D. Rifaximin is a rifamycin-based oral non-absorbable antibiotic that has a strong in vitro antimicrobial effect against aerobic and anaerobic gram-positive and gram-negative bacteria.⁸⁸ Rifaximin has high solubility in the presence of bile acids, and poorly systemic absorption.^{85,89,90} It may result in inhibition of a broad spectrum of bacteria in the small intestine, without a systemic adverse effect.⁹¹

Many previous studies reported that rifaximin treatment in SIBO and IBS patients had significant benefits compared with placebo.^{87,92-94} In the 2 largest phase 3 trials involving people with non-constipated IBS (TARGET 1 and 2), treatment with rifaximin 550 mg 3 times a day for 2 weeks achieved adequate alleviation of the global IBS symptoms (40.7% vs 31.7% for placebo, pooled; $P < 0.001$) and bloating (40.2% vs 30.3% for placebo, pooled; $P < 0.001$) during the first 4 weeks after treatment.⁸⁷ In addition, a

meta-analysis of 5 RCTs of rifaximin for IBS, including TARGET 1 and 2, reported that rifaximin was more efficacious than placebo for global IBS symptom alleviation (OR, 1.57; 95% CI, 1.22) and bloating alleviation (OR, 1.55; 95% CI, 1.23-1.96).⁹⁴

Although it is generally acknowledged that rifaximin leads to short-term clinical improvements in some IBS patients, there are several points to be considered before promoting the widespread use of rifaximin. First, a less-than-half response rate and a 9% therapeutic gain means that several administrations are needed to treat roughly 11 patients.⁹⁵ To prevent antibiotic misuse, a specific predictor of the response to antibiotic treatment in IBS patients is needed. The potential candidates for the predictor are diagnostic tests for SIBO, including breath tests and analysis of the upper-gut aspirates. In previous studies, normalization of the results of the breath test in IBS patients after antibiotic therapy has been shown to be correlated with a successful response to antibiotic therapy.^{86,92,93,96} The predictive value of a positive lactulose breath test has been disappointing, however, in selecting patients who will respond.⁹⁷⁻⁹⁹ In a recent prospective study that used upper-gut aspiration culture for diagnosing SIBO, IBS patients with SIBO had greater symptom alleviation than patients without SIBO (87.5% vs 25%) 1 month after the administration of antibiotics.¹⁰⁰ The technique of upper-gut aspiration, however, has limited application in clinical practice due to its invasiveness and expensiveness. Further study will be required to identify the biomarker-based strategies that will enrich the likelihood of a response to antibiotics in IBS patients.⁹⁵

Although a recent study suggested that long-term rifaximin use for hepatic encephalopathy is safe and tolerable,¹⁰¹ it must be considered that excessive rifaximin use may lead to resistance and adaptation among pathogens. There is emerging evidence that rifaximin use can select rifaximin-resistant strains of bacteria, such as *Clostridium difficile* and *Escherichia coli*.^{102,103} Furthermore, rifaximin is a structural analog of rifampin, which is used for treating several infections, such as tuberculosis and methicillin-resistant *Staphylococcus aureus*.¹⁰⁴ In a prospective study, rifampin-resistant human-skin staphylococci emerged after oral intake of rifaximin by 20 healthy volunteers, and these isolates were still found on the hands and lower arms after 9 weeks.¹⁰⁴ There is a consensus that rifaximin may be a treatment of choice for some IBS patients. Before the promotion of the wide use of rifaximin, however, further studies are still needed for the identification of the subpopulation of IBS patients who may best benefit from rifaximin use.

Fecal Microbiota Transplantation

In people with disease related to dysbiosis, reconstituting the normal gut microbiota is essential to the treatment of the disease. The administration of a fecal suspension containing the normal gut microbiota from a healthy donor to the gut of the dysbiosis patient, known as fecal microbiota transplantation (FMT), can restore the phylogenetic diversity and microbiota more typical of a healthy person. As the disrupted gut microbiota is a key factor in the pathogenesis of *C. difficile* infection (CDI), FMT is increasingly used for recurrent or severe CDI.¹⁰⁵⁻¹⁰⁷ In a recent systemic review involving 516 patients with recurrent CDI,¹⁰⁸ the overall success rate of FMT was reported as 85% for recurrent CDI and 55% for refractory cases. Although the evidence for such is limited, FMT for CDI seems safe. In 2 RCTs,^{106,109} only mild adverse events such as diarrhea, cramping, belching, nausea, abdominal pain, and bloating were reported.¹⁰⁶ In addition, the restored gut microbiota became similar to those of the donors, and persisted in a durable fashion after FMT.^{106,110,111} Thus, FMT is being applied to several diseases related with dysbiosis other than CDI.¹¹² Although not nearly as effective as in CDI, FMT has also shown promising results in IBD.¹¹³⁻¹¹⁵ A far more complex microbial basis of the pathogenesis in IBD than in CDI, however, appears to need the best methodology, including ideal donor and recipient, mode of delivery, dose, and timing.¹¹⁶

The increasingly appreciated role of gut microbiota in the pathogenesis of FBDs and the imperfect current treatment can promote the use of FMT in selected patients with FBDs.¹¹⁷⁻¹¹⁹ To date, few case series have reported outcomes of FMT for constipation and IBS,^{120,121} but the results are promising. In a recent small study of FMT for refractory IBS (total of 13 patients: 9 IBS-D, 3 IBS-C, and 1 mixed IBS), a fecal suspension was infused into the distal duodenum or proximal jejunum via upper endoscopy. During a mean 11-month follow-up, resolution or alleviation of the symptoms was observed in 70% of the patients. In addition, the overall well-being was improved in 46% of the patients. The outcomes were not influenced by the donors, and only transient increased flatus was reported as an adverse event. These observations indicate that reconstituting the normal gut microbiota via FMT is a promising novel approach for FBD treatment, but further large studies, including well-designed RCTs, are mandatory to confirm that FMT is effective for FBD treatment. Although FMT appears to be well tolerated, a more specific modulation of the gut microbiota should be pursued in the future. Thus, the change in the gut microbiota in

patients with FBDs after FMT also has to be investigated to characterize the specific microbial role of FMT for FBD treatment.

Summary and Conclusion

Dietary factors have strong effects on the gut microbiota. The composition of the gut microbiota, as affected by various diets, is related to the development of FBDs. At present, whether FBDs can be effectively treated or prevented by altering the composition of the gut microbiota through dietary modulation is still unknown. More research involving animal models, as well as robust epidemiologic and well-controlled interventional studies involving human beings are required.

Some probiotic strains that have been proven to be effective through RCTs can be a safe and promising treatment modality in FBD patients with IBS, and seems to be more effective in IBS-D than in IBS-C. Differentiation of the efficacy-proven strains and careful selection of the target patients based on both the symptoms and the properties of the available strains are important prerequisites of the clinical application of probiotics. A combination of specific probiotics and prebiotics (ie, synbiotics) may be an effective treatment option for IBS-C or FC in the future. Fermented milk products containing high concentrations of FODMAPs can aggravate the symptoms of IBS.

There is a consensus that rifaximin may be a treatment of choice for some IBS patients, but further studies are still warranted to identify the IBS patients who can best benefit from rifaximin use.

Reconstituting the normal gut microbiota via FMT is a promising novel approach for FBD treatment. Further large studies, however, including well-designed RCTs, are mandatory to confirm that FMT is effective for FBD treatment.

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