Current perspectives on irritable bowel syndrome: a narrative review

Mariko Hojo and Akihito Nagahara

Abstract
The pathophysiology of irritable bowel syndrome (IBS) has not yet been fully elucidated. We reviewed articles addressing IBS that have been published in the last 2 years and selected papers related to IBS pathophysiology and treatment. Studies of intestinal bacteria, low-grade mucosal inflammation, and increased mucosal permeability—factors involved in the pathophysiology of IBS—have been conducted. In addition, the involvement of intestinal bacteria in IBS pathology has been clarified; many studies of treatments related to intestinal bacteria have been reported. Moreover, several studies address the effect on IBS of antidepressants and psychotherapy through the brain–gut axis. The contents of these papers are described in this narrative review.

Keywords
Irritable bowel syndrome, pathophysiology, treatment, intestinal bacteria, mucosal inflammation, mucosal permeability, antidepressant, psychotherapy

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Introduction
The pathophysiology of irritable bowel syndrome (IBS) has not yet been fully elucidated. Many studies on the pathophysiology and treatment of IBS are ongoing and the publication of review articles is underway.1 In recent years, intestinal bacteria, low-grade mucosal inflammation, and increased mucosal permeability have been confirmed to be involved in IBS pathophysiology and studies related to these factors have been actively conducted. Specifically, the involvement of intestinal bacteria in IBS pathology has been confirmed and many studies of treatments addressing intestinal bacteria have been reported. Moreover, several studies on the effects on IBS of antidepressants and psychotherapy via the
brain–gut axis have been conducted. We created this narrative review to examine recent articles addressing this topic.

**Methods**

We used the search term “irritable bowel syndrome” to search articles in PubMed from July 2019 to September 2021. More than 2000 papers were extracted. Among the articles published during the search period, we selected 18 papers of interest related to the pathophysiology and treatment of IBS and explained the contents of these articles.2–19

**Pathophysiology of IBS**

Genetic factors are involved in the pathology of IBS.20 A comprehensive analysis of colonic mucosal microRNAs was performed by Mahurkar-Joshi et al.2 The authors performed reverse transcription polymerase chain reaction on biopsy specimens of the sigmoid colons of IBS patients and healthy participants to study genes that were differentially expressed between IBS patients and healthy controls. Results indicated that the expression levels of miR-219a-5p and miR-338-3p were reduced in IBS patients. Functionally, decreased expression of miR-219a-5p was associated with a decrease in trans-epithelial electrical resistance and an increase in the permeability of intestinal epithelial cells. Decreased expression of miR-338-3p was associated with changes in the expression of genes involved in the mitogen-activated protein kinase signaling pathway associated with visceral hypersensitivity. Further studies on qualitative and quantitative changes in gene expression in IBS patients are expected in the future.

Gut microbiota is involved in the pathology of IBS.21,22 Some patients with infectious enteritis subsequently develop post-infectious IBS (PI-IBS).23 Furthermore, some patients who suffer from *Campylobacter* enteritis are reported to develop PI-IBS.24 Although some *Campylobacter jejuni* strains cause disease,25,26 the genes and pathogenic characteristics that promote IBS development remain unclear. Using pangenome-wide association studies and phenotypic assays, Peters et al.3 examined differences between *Campylobacter jejuni* strains isolated from patients who subsequently did or did not develop PI-IBS. The results showed that mutations in the stress response gene (*Cj0145_phoX*), adhesive protein gene (*Cj0628_CapA*), and core biosynthetic pathway gene (biotin: *Cj0308_bioD*; purine: *Cj0514_purQ*; isoprenoid: *Cj0894c_ispH*) were involved in the development of PI-IBS. The phenotypic assay further indicated that strains isolated from IBS-affected patients adhered to and invaded intestinal cells more powerfully and stimulated more interleukin(IL)-8 and tumor necrosis factor α (TNFα) secretion from intestinal cells than strains isolated from non-IBS-affected patients. In addition, Peters et al.3 developed a risk score for developing PI-IBS using 22 genomic markers including four markers derived from the predicted heme oxidase gene linked to virulence.27 The results of this study demonstrated that specific *Campylobacter* genotypes increased in vitro pathogenicity and the risk of developing PI-IBS.

Psychological stress and gut microbiota play important roles in the pathophysiology of IBS.28,29 Mental stress may further affect not only intestinal bacteria but also intestinal mucosal permeability.30 Given intestinal bacteria are involved in IBS pathophysiology, probiotic treatment may be effective in IBS. The mechanism by which probiotic treatment affects the psychological stress-induced change in intestinal mucosal permeability and activation of the immune system remains unclear. In an animal study, Wang et al.4 examined how the
probiotic *Bifidobacterium bifidum* G9-1 (BBG9-1) affects macrophages and the colonic mucosal permeability in IBS model rats that were subjected to stress from maternal separation. The mucosal permeability of the colonic epithelium was significantly higher (*P* < 0.05), claudin-4 expression was significantly reduced (*P* < 0.05), the number of CD80-positive M1 macrophages in the colonic mucosa was significantly increased (*P* < 0.01), and the expression levels of IL-6 and interferon-γ (IFN-γ) were significantly elevated (*P* < 0.05 and *P* < 0.01, respectively) in the maternal separated rats compared with control rats. Treatment with BBG9-1 significantly counteracted the increase in M1 macrophages and IL-6 and IFN-γ expression in the colonic mucosa of maternal separated rats. Treatment neutralized both the increase in mucosal permeability and the decline in claudin-4 expression in the colons of maternal separated rats. These results indicate that BBG9-1 acts protectively against increases in colonic mucosal permeability and M1 macrophages caused by psychological stress. Furthermore, IL-6 and IFN-γ significantly reduced the trans-epithelial electrical resistance of Caco2 cells in vitro, suggesting that *Bifidobacterium* strains may improve cytokine-stimulated epithelial cell barrier disruption.

The involvement of the gut virome in IBS pathophysiology has also been studied. Following a metagenomic analysis of DNA and RNA viruses using stool samples from healthy individuals and IBS patients, Mihindukulasuriya et al. reported that the gut virome was stable over time but varied by IBS subtype. The authors reported that the gut virome could be affected by diet and could affect host functions through interactions with gut bacteria or changes in host gene expression.

Eosinophils are multi-functional granulocytes. Eosinophils in the intestinal mucosa contain substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and corticotropin-releasing hormone (CRH). Also known as corticotropin-releasing factor, CRH plays an important role in the stress response and is involved in IBS pathophysiology. The presence of CRH in intestinal mucosal eosinophils of IBS patients suggests that mucosal eosinophils play a role in IBS pathophysiology. Salvo-Romero et al. reported that mucosal eosinophil degranulation was observed to a greater extent in diarrhea-predominant IBS (IBS-D) patients than in healthy controls, that IBS-D patients had an increased level of CRH in cytoplasmic granules compared with healthy controls, and that the amount of CRH in cytoplasmic granules correlated with the clinical severity of IBS, life stress, and a depressive score. Furthermore, the authors reported that substance P and carbachol enhanced the secretory activity of eosinophils and increased CRH synthesis and release from eosinophils. The results of this study demonstrated that eosinophils in the intestinal mucosa may affect the pathophysiology of IBS-D by synthesizing and releasing CRH. Recently, eosinophils in the colonic mucosa were reported to express the μ-opioid receptor, αβ-endorphin that binds to the μ-opioid receptor with high affinity, and cannabinoid receptor-2. Eosinophils may be involved in the opioid and cannabinoid systems that regulate physiological functions such as intestinal perception and movement.

In addition to CRH, oxytocin is involved in IBS pathophysiology. Tsushima et al. showed that oxytocin antagonists enhanced visceral hypersensitivity to colorectal distention stimuli in animal models and increased anxiety-like behavior. The authors explained that colorectal distention stimuli activate oxytocin neurons in the
paraventricular nucleus and the neurons containing CRH in the central nucleus of the amygdala, and that neuron activation was further enhanced by the administration of an oxytocin antagonist in addition to the strong colorectal distention stimuli. The authors further observed that neurons in the anterior cingulate cortex are activated by strong colorectal distention stimuli and that the activation is suppressed by the addition of a high-dose oxytocin antagonist. These results indicate that oxytocin suppresses CRH-containing amygdala neurons and promotes the anterior cingulate cortex. Further studies on brain activity and the roles of CRH, oxytocin, the anterior cingulate cortex, and the amygdala may lead to the development of methods for controlling visceral hypersensitivity.

Treatment of IBS

Many studies report that IBS symptoms are related to diet. Dietary content that tends to cause IBS symptoms includes lipids, caffeine, and spices. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) are difficult to decompose, are absorbed in the small intestine, and are fermented and decomposed by bacteria in the colon. Although several studies report the usefulness of low FODMAP diets for IBS patients, the usefulness of these diets is still debated. Wang et al. conducted a meta-analysis to determine if a low FODMAP diet was useful for improving IBS symptoms. The authors selected 10 randomized controlled trials (511 participants) that compared a low FODMAP diet to control diets including high FODMAP, traditional IBS, and normal diets. When seven of these studies were combined, the low FODMAP diet was associated with better improvement of general IBS symptoms compared with the control diet (n = 420; relative risk = 1.54; 95% CI: 1.18–2.00; I2 = 38%). The results further indicated that the low FODMAP diet had a considerable effect on stool shape and the frequency of stools per day and may be more effective in patients with diarrhea-predominant IBS. Study limitations cited included the small sample size of each study, the lack of assessment of the intervention effectiveness by IBS subgroup in several studies, and the lack of symptom evaluation using a unified evaluation scale. Therefore, this meta-analysis appears to provide moderate-quality evidence of the usefulness of a low FODMAP diet in improving IBS symptoms. Concurrently, Black et al. conducted a network meta-analysis comparing low FODMAP diets with control diets including high FODMAP, traditional IBS, and regular diets. In a study of 13 randomized controlled trials (944 participants), a low FODMAP diet was ranked first in achieving overall IBS symptom improvement (relative risk = 0.67; 95% CI: 0.48–0.91, P = 0.99), and was shown to be more useful than any other diet. A meta-analysis by Hahn et al. further demonstrated that a low FODMAP diet was useful in improving IBS symptoms, a finding supported by accumulating evidence. However, the decreased function of the sucrase-isomaltase complex involved in sucrose and starch degradation is reportedly related to IBS pathophysiology. In IBS patients with a low-functioning sucrase-isomaltase complex, low FODMAP diets that do not limit sucrose intake are less effective than in IBS patients with normal function. Randomized controlled trials on the effectiveness of low FODMAP diets have not been conducted in Japan. Further studies are needed to establish whether a low FODMAP diet can be considered a treatment for IBS.

Furthermore, in a study of dietary patterns, gut inflammatory markers, and the relationship between gut microbial composition and function, Bolte et al. observed
that habitual dietary content affected the human gut ecosystem and the induction and suppression of inflammation; similar relationships were observed in IBS patients. The authors noted that dietary strategies targeting the gut flora may be useful in alleviating and preventing gut inflammation.

Several studies investigated the effectiveness of probiotics in IBS.\(^{41-43}\) Wen et al.\(^{14}\) conducted a meta-analysis of 17 randomized controlled trials (1469 participants) of adults with constipation-predominant IBS who were randomized to a probiotic or placebo group. After pooling the results of 11 studies, the authors observed that the probiotic group had a significantly higher weekly defecation frequency than the placebo group; probiotics increased stool frequency by 1.29 bowel movements/week (95% CI: 0.69–1.89 bowel movements/week; \(P < 0.0001\)). After pooling the results of 10 studies, the probiotic group reported having significantly softer stools than the placebo group (\(P = 0.0001\)). In addition, pooled results from three studies indicated that the probiotic group had significantly shorter intestinal transit times than the placebo group (\(P = 0.004\)). The authors concluded that studies with appropriately sized samples are needed to determine the optimal bacterial species and strain and the amount and duration of probiotic use. Thus, further research is required to support whether probiotics can be regarded as a treatment option for IBS.

Since the 2013 report of a randomized controlled trial investigating fecal microbiota transplantation (FMT) for the treatment of \textit{Clostridium difficile} infection,\(^{44}\) FMT treatment has been used to treat various diseases.\(^{45-51}\) Reports of FMT treatment for IBS have increased in recent years and meta-analyses have been reported, but consensus has not yet been reached.\(^{50,51}\) Studies of the effectiveness of multiple FMTs have since emerged.\(^{54-56}\) In recent years, a double-blind, randomized controlled trial of donor and placebo stool (autologous stool) transplantation was conducted in IBS patients with abdominal distension as the main symptom.\(^{15}\) At the 3-month post-transplantation assessment, IBS symptoms improved in 56% of patients who underwent donor fecal transplants while only 26% of patients who received placebo fecal transplants showed improvement (\(P = 0.03\)). Pre-transplanted fecal samples from treatment responders had greater bacterial flora diversity than samples from non-responders (\(P = 0.04\)), and the composition of fecal flora was significantly different between responders and non-responders (\(P = 0.04\)). At the evaluation 1 year post-transplantation, 21% of patients who received donor stool had no relapse of symptoms, while only 5% of patients who received placebo stool had no relapse. When a second course of FMT treatment was provided to symptomatic patients, 67% of the patients who responded to the initial course of treatment and 0% of non-responding patients showed symptomatic improvement. The results of this study suggest that FMT treatment is useful for some IBS patients and its effectiveness may be related to gut bacterial flora before FMT treatment. Moreover, findings indicate that the fecal flora characteristics before FMT treatment may be biomarkers for selecting responders to FMT treatment. Future studies can further identify the characteristics of patients who respond to FMT treatment.

Despite many reports on the use of tricyclic antidepressants and selective serotonin reuptake inhibitors for the treatment of IBS,\(^{57}\) only a few studies report on the use of a serotonin-norepinephrine reuptake inhibitor (SNRI) and a noradrenergic and specific serotonergic antidepressant (NaSSA).\(^{58,59}\) Sharbafchi et al.\(^{16}\) conducted a double-blind randomized trial in which the SNRI venlafaxine or placebo was administered to 33 patients with
moderate-to-severe IBS. The authors reported that the venlafaxine group showed significant improvement in the severity of symptoms compared with the placebo group (P < 0.001). In Khalilian et al.'s double-blind, randomized controlled trial, the NaSSA mirtazapine or placebo was administered to 67 patients with diarrhea-predominant IBS. The mirtazapine group showed significant improvement in symptom severity compared with the placebo group (P = 0.002). Appropriately sized future studies are required to verify the results of these studies.

Krouwel et al. conducted a meta-analysis to elucidate the effects of hypnotherapy on IBS and predictors of its effects. By pooling data from seven reports, the authors observed that hypnotherapy reduced IBS symptoms (standardized mean difference 0.24, [−0.06, 0.54], I² = 66%). Subgroup analysis showed that higher volumes of intervention (i.e., total treatment time of 6 or more hours and eight or more sessions) provided significantly more symptom relief than lesser volumes (P = 0.0001). In addition, frequent treatment (e.g., more than once a week) and group treatment were shown to be potentially effective. The meta-analysis indicated that a high volume of intervention was one of the predictors of the therapeutic effect of hypnotherapy; however, the optimal number of sessions remained unclear. Therefore, Hasan et al. randomly assigned six or 12 sessions of gut-focused hypnotherapy to 489 IBS patients, with 394 patients completing the assigned number of sessions. Results indicated that a course of six sessions of gut-focused hypnotherapy was not inferior to 12 sessions and that the course of six sessions had a lower percentage of dropouts. The unknown long-term effect of six sessions of hypnotherapy was cited as a limitation of the study. Further studies are required before hypnotherapy is established as a treatment for IBS.

Conclusion
This review presented topics related to IBS pathophysiology and treatment. Genetic factors, infectious enteritis, gut microbiota, stress, increased mucosal permeability, low-grade mucosal inflammation, and endocrine substances have been reported to contribute to IBS pathophysiology. While these factors are known to be involved in IBS pathology, further research is required to understand their role in disease pathophysiology. Furthermore, we reviewed studies of IBS treatments such as probiotics, FMTs, and low FODMAP diets that affect the gut microbiota. Previous studies have shown that treatments that affect gut microbiota are not equally effective in all IBS patients; future studies must identify the IBS characteristics these treatments are useful for. Finally, this review explains the findings of reports on the use of antidepressants and hypnotherapy in IBS. Although these approaches may be effective, further studies are required to establish psychotherapy as a recommended treatment for IBS.

Author contributions
MH designed the work and drafted the manuscript. MH and AN reviewed and approved the final version of the manuscript.

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ORCID iD
Mariko Hojo https://orcid.org/0000-0001-9671-5585
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