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REVIEW

Microbiome and Its Role in Irritable Bowel Syndrome

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Abstract

Irritable bowel syndrome (IBS) is an extremely common and often very debilitating chronic functional gastrointestinal disorder. Despite its prevalence, significant associated healthcare costs, and quality-of-life issues for affected individuals, our understanding of its etiology remained limited. However, it is now evident that microbial factors play key roles in IBS pathophysiology. Acute gastroenteritis following exposure to pathogens can precipitate the development of IBS, and studies have demonstrated changes in the gut microbiome in IBS patients. These changes may explain some of the symptoms of IBS, including visceral hypersensitivity, as gut microbes exert effects on the host immune system and gut barrier function, as well as the brain–gut axis. Microbial differences also appear to underlie the two main functional categories of IBS: diarrhea-predominant IBS (IBS-D) is associated with small intestinal bacterial overgrowth, which can be diagnosed by a positive hydrogen breath test, and constipation-predominant IBS (IBS-C) is associated with increased levels of methanogenic archaea, which can be diagnosed by a positive methane breath test. Mechanistically, the pathogens that cause gastroenteritis and trigger subsequent IBS development produce a common toxin, cytolethal distending toxin B (CdtB), and antibodies raised against CdtB cross-react with the cytoskeletal protein vinculin and impair gut motility, facilitating bacterial overgrowth. In contrast, methane gas slows intestinal contractility, which may facilitate the development of constipation. While antibiotics and dietary manipulations have been used to relieve IBS symptoms, with varying success, elucidating the specific mechanisms by which gut microbes exert their effects on the host may allow the development of targeted treatments that may successfully treat the underlying causes of IBS.

Keywords Irritable bowel syndrome · Gut microbiome · Acute gastroenteritis · Small intestinal bacterial overgrowth · Brain-gut axis · Diet · Antibiotics

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Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by abdominal pain and altered bowel habits, either diarrhea (IBS-D), constipation (IBS-C), or altering between diarrhea and constipation (IBS-M). Approximately 13% of the world's population suffers from IBS symptoms [1], which results in increased consultations, diagnostic procedures, and surgeries. IBS is also associated with increased medication consumption, reduced quality of life, and high rates of absenteeism from work and school, and the costs of IBS in the USA alone have been estimated at over $30 billion [2].

Despite the prevalence and burden of IBS, its pathobiology has remained elusive. Early studies focused on gastrointestinal motor disturbances including changes in intestinal transit and abnormal contractions [3]. Subsequent studies found that many IBS patients experience pain from rectal balloon distention at lower thresholds than healthy controls (i.e., visceral hypersensitivity). Increasing evidence over the past decade suggests that the microbiome may contribute significantly to these findings in IBS. Early recognition that IBS frequently develops after an episode of infectious gastroenteritis led investigators to explore the role of bacteria in the pathophysiology of IBS. Uncovering this role requires the understanding of two parallel paths of research into post-infectious IBS and intestinal dysbiosis, which later merge into a single hypothesis (Fig. 1).

Post-infectious IBS

Prevalence

Reports of post-infectious IBS are not new, although until recently these descriptions were sporadic. In the 1960s, Chaudhary and Truelove described what was then known as "irritable colon syndrome" following infectious gastroenteritis [4]. In 1994, McKendrick and Read reported the development of IBS following two outbreaks of *Salmonella* in the UK [5]. Subsequently, multiple infectious gastrointestinal outbreaks have been studied, with the incidence of post-infectious IBS ranging from 3.7 to 36% and lasting up to 6 and 8 years after the acute illness [6]. In addition to typical acute gastroenteritis pathogens, even more exotic pathogens are being linked to IBS as well, such as spirochetes [7].

A recent meta-analysis of 45 studies that prospectively followed infectious outbreaks found that the pooled incidence of IBS was 10.1% at 3 or more months after acute gastroenteritis and 14.5% at more than 12 months after acute gastroenteritis [6]. The risk of IBS was 4.2-fold higher in patients who had acute gastroenteritis in the past 12 months than in those who did not [6]. Several factors increased the likelihood of developing IBS (Table 1). Notably, the severity of acute gastroenteritis and female sex were strong predictors. Although the reasons for the higher prevalence of IBS in women remain unproven, a recent genome-wide

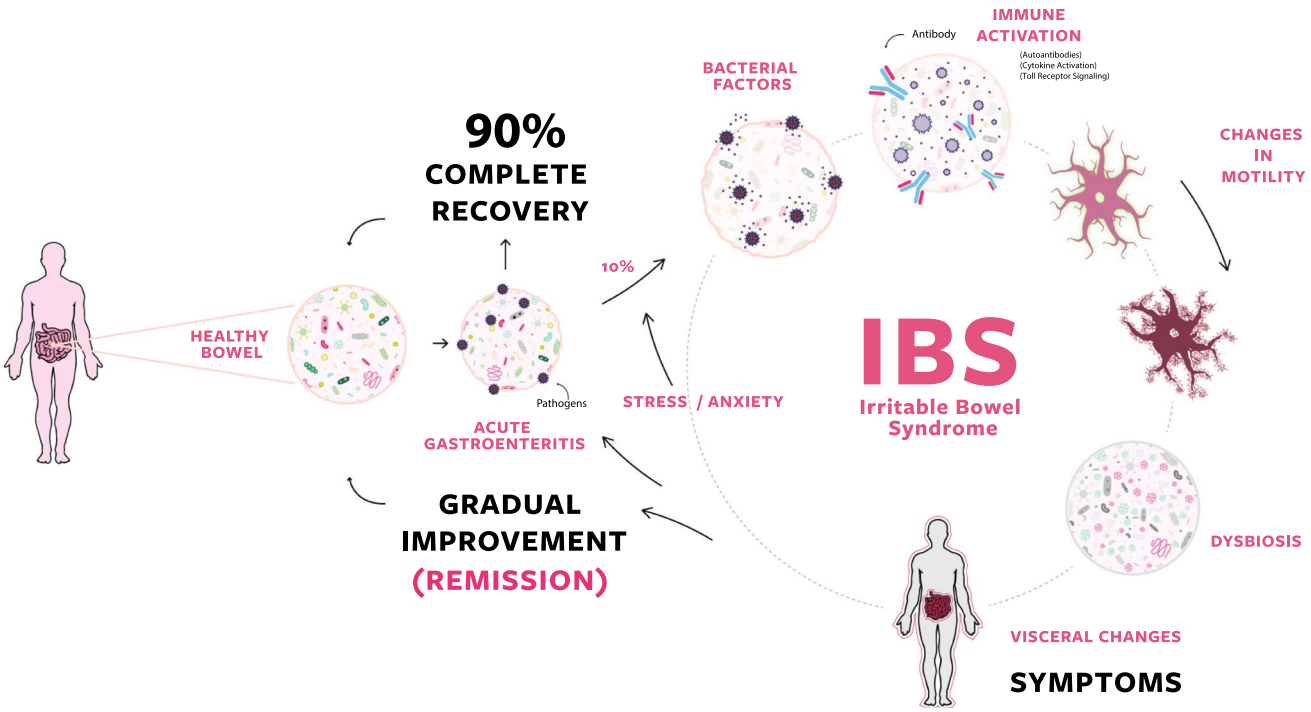

Fig. 1 Microbial hypothesis in irritable bowel syndrome

Table 1 Risk factors for the development of post-infectious IBS following acute gastroenteritis. Adapted from Klem et al. Gastroenterology [6]

Risk factor	Pooled OR at 95% CI (range)
Host-related	
Female gender	2.19 (1.57–3.07)
Anxiety	1.97 (1.32–2.94)
Depression	1.49 (1.17–1.90)
Somatization	4.05 (2.71–6.03)
Neuroticism	3.26 (1.62–6.55)
Smoking	1.15 (0.90–1.46)
AGE-related	
Abdominal pain	3.26 (1.30–8.14)
Antibiotic use	1.69 (1.20–2.37)
Bloody stool	1.86 (1.14–3.03)
Duration of > 7 days	2.62 (1.48–4.61)
Fever	1.21 (0.66–2.23)
Weight loss	1.69 (0.87–3.25)

association study (GWAS) by Bonfiglio et al. found an association between variants at the locus 9q31.2 and the risk of IBS in women, a region previously associated with conditions and traits influenced by sex hormones [8].

Psychological Factors

Although IBS is frequently associated with stress and anxiety [9], it has been unclear to what extent these contribute to the development of IBS, or vice versa. Evidence from studies in animal models, e.g., the *Citrobacter rodentium* mouse model [10], indicates stress may affect the gut microbiota, increase gut motility [11], and augment the risk of developing post-infectious symptoms. Recently, a study of deployed US military personnel found that, despite significant psychological stress in combat zones, acute gastroenteritis during deployment rather than stress was the most important risk factor for IBS development [12]. Furthermore, recent evidence indicates that in approximately two-thirds of IBS cases, psychological distress develops after the onset of gastrointestinal symptoms [13].

Post-infectious IBS Changes the Microbiome

Following the emerging data that linked IBS to acute gastroenteritis, animal models were developed. These included the above-described *Citrobacter rodentium* mouse model [10], as well as the *Trichinella spiralis* mouse model that has been used to study smooth muscle hypercontractility following parasite infection [14]. While these models have provided valuable insights, neither *Citrobacter* nor *Trichinella* are common causes of human acute gastroenteritis or post-infectious IBS in the USA. In another model, Sprague–Dawley rats were infected with *Campylobacter jejuni* [15], one of the most common causes of bacterial gastroenteritis in the USA. After recovery from the initial acute infection, most animals developed altered stool form, increased rectal lymphocytes [15], reduced deep muscular plexus interstitial cells of Cajal, and small intestinal bacterial overgrowth [16]. These findings mirrored findings in humans with post-infectious IBS [17]. Interestingly, small intestinal bacterial overgrowth in humans can result from reductions in migrating motor complexes [18] for which the deep muscular plexus interstitial cells of Cajal are the pacemaker cells.

This new animal model was an important tool to study the development of IBS following acute gastroenteritis. Since *C. difficile*, *C. jejuni*, *Salmonella*, *Escherichia coli*, and *Shigella* can all cause IBS [6], identifying a common factor became an important goal. One commonality was the production of cytolethal distending toxin (Cdt). Pokkunuri et al. showed that animals infected with a genetically modified *C. jejuni* lacking *CdtB* had fewer symptoms (i.e., altered bowel habits) and less inflammation (i.e., rectal lymphocytes [17]) compared to animals exposed to wild-type *C. jejuni* [19]. These results suggested the CdtB toxin was required for the development of IBS-like phenotypes.

Subsequent studies found that antibodies to CdtB cross-react with vinculin [20], an intracellular cytoskeletal protein that is an important component of cell adhesion and plays a key role in neuronal cell motility and contractility [21], particularly in the gastrointestinal tract. Data suggest that exposure to CdtB leads to autoimmunity to vinculin [20], supporting an earlier hypothesis that autoimmunity may play a role in functional gastrointestinal disorders [22].

The clinical significance of these discoveries is highlighted by the finding that anti-CdtB and anti-vinculin antibodies occur more commonly in IBS-D as compared to other conditions that cause diarrhea, including inflammatory bowel disease (IBD) and celiac disease [23]. When both antibodies are positive, an IBS-D diagnosis can be reached more confidently [23]. However, sensitivity remained low at approximately 50%, likely due to the heterogeneous nature of IBS-D pathophysiology. The utility of these antibodies in diagnosing IBS has been validated in several independent studies performed in European [24], Latin American [25], and US military [26] populations.

Antibiotics

Studies have also suggested that prior antibiotics are a risk factor for IBS. In a case-controlled study, antibiotic use in the previous year was associated with a three-fold increased

risk of developing IBS [27]. In another case-controlled study, 83% of patients with new-onset functional GI symptoms reported antibiotic use with an odds ratio of 1.95 (95% CI: 1.2–3.0, $p = 0.005$) [28].

Role of Intestinal Dysbiosis in IBS

The concept that the intestinal microbiome was associated with human disease led investigators to study whether alterations in the microbiome could be identified in IBS, and whether these contributed to, or were the result of, the IBS development. Numerous studies have been performed using varying techniques (quantitative PCR (qPCR), 16S rRNA denaturing gradient gel electrophoresis (DGGE), phylogenetic microarrays, and 16S rRNA gene sequencing) and sample types (fecal samples, duodenal mucosa brush samples, duodenal aspirates, and colonic/rectal mucosal biopsy samples) (Table 2). Moreover, some compared IBS subjects to healthy controls, while others examined specific IBS subtypes. Comparing these studies, several [29–34], but not all [35], identified lower microbial diversity or richness in IBS subjects versus healthy controls. At the phylum level, some found an increase in Firmicutes-to-Bacteroidetes ratio in IBS subjects, including Rajilic-Stojanovic et al. who also found decreased Bifidobacterium [36] and Jeffery et al. who also found increased Actinobacteria in IBS samples [31]. In contrast, Ng et al. found increased Bacteroidetes abundance and decreased Actinobacteria abundance in IBS subjects versus healthy controls, with probiotic treatment reducing the genus *Bacteroides* to levels similar to controls [32]. A recent meta-analysis of stool qPCR studies identified consistent findings of lower levels of *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii* in IBS subjects [37]. Using a machine learning procedure, a recent study identified a microbial profile in patients with severe IBS characterized by decreased microbial richness, lower levels of exhaled methane, and a *Bacteroides*-enriched enterotype [38].

One of the stronger links between IBS and the intestinal microbiota is the finding that the transfer of stool from IBS-D patients to animals induces changes similar to those in IBS, including altered intestinal motility, innate immune-activation and increased intestinal permeability, and visceral hypersensitivity [39]. IBS patients also appear to have increased expression of intestinal Toll-like receptors (TLRs) [40, 41], which are important mediators of intestinal immune response to gut microbes—specifically, TLR4 is implicated in recognition of bacterial lipopolysaccharide (LPS) and TLR5 is implicated in flagellin recognition [42]. Pike et al. suggested that differences in host immune responses may predict the likelihood of developing IBS, with or without antecedent acute gastroenteritis, and concluded that combining cytokine profiles with microbiome-directed antibodies might provide optimal results [26]. They also found a strong association between anti-vinculin antibody levels and development of post-*Campylobacter* IBS [26].

Small Intestinal Bacterial Overgrowth and IBS

Many, but not all, studies have reported a greater prevalence of small intestinal bacterial overgrowth in IBS versus controls based on either glucose or lactulose breath testing [43]. Meta-analyses revealed that breath testing is abnormal in IBS subjects more often than in healthy controls (pooled OR 3.45 (95% CI 0.9–12.7) or 4.7 (95% CI 1.7–12.95)), depending on the criteria used to define a positive test [43]. In comparison, only a handful of studies used small bowel cultures to determine the presence of small intestinal bacterial overgrowth. Posserud et al. showed that coliforms were much more common in duodenal aspirates from IBS subjects versus healthy controls [44]. However, using older definitions of small intestinal bacterial overgrowth ($> 10^5$ cfu/mL), these differences were not significant. Another study found small intestinal bacterial overgrowth was far more predominant in IBS patients than in non-IBS patients undergoing endoscopy for other reasons [45]. QPCR and deep sequencing of small bowel aspirates from IBS subjects and controls confirmed these findings [33].

Recent data suggest that elevated methane gas production, generated predominantly by archaeal species, can influence intestinal motor activity and leads to intestinal slowing and constipation [46, 47]. In humans, the predominant archaeon and methane producer is *Methanobrevibacter smithii [*48]. In a double-blind, randomized, placebo-controlled trial [49], a combination of rifaximin and neomycin could be used to eradicate methane on breath test in up to 85% of subjects, resulting in significant improvements in gastrointestinal symptoms including constipation severity, straining, and bloating [49]. A recent consensus now considers methane (as a surrogate for excess intestinal colonization with methanogens) as important in the assessment of constipation and IBS-C [50].

Brain–Gut–Microbiome Axis

The brain–gut axis has been widely described as important to the understanding of IBS [3]. IBS is associated with alterations in gut motility, gut barrier function, immune regulation, and visceral hypersensitivity, all of which can be affected by the gut microbiome [42, 51, 52]. For example, increased serum levels of bacterial LPS and anti-flagellin antibodies have been demonstrated in IBS-D subjects, indicating impaired gut barrier function

Table 2 Microbiome analysis studies in IBS

Study	Subjects, samples, and techniques	Principal findings
Kerckhoffs et al. [78]	Fecal and duodenal mucosa brush samples 41 IBS and 26 healthy controls FISH; qPCR for Bifidobacteria	Lower Bifidobacteria counts in duodenum and fecal samples in IBS
Codling et al. [29]	Fecal and colonic mucosa samples 47 IBS and 33 healthy controls 16S rRNA DGGE[a]	Lower microbial diversity in IBS
Kerckhoffs et al. [79]	Fecal and duodenal mucosa brush samples 37 IBS and 20 healthy controls 16S rRNA DGGE[a] and qPCR	Higher levels of *Pseudomonas aeruginosa* in duodenal and fecal samples in IBS
Ponnusamy et al. [35]	Fecal samples 11 IBS and 8 non-IBS 16S rRNA DGGE[a] and qPCR	Higher diversity of total bacteria, Bacteroidetes and Lactobacillus in IBS Lower diversity of Bifidobacter and *Clostridium coccoides* in IBS
Rajilic-Stojanovic et al. [36]	Fecal samples 62 IBS (varied subtypes) and 46 healthy controls Phylogenetic microarray and qPCR	Twofold increase in Firmicutes-to-Bacteroidetes ratio in IBS 1.5-fold increase in Dorea, Ruminococcus, and *Clostridium* spp. 1.5-fold decrease in *Bifidobacterium* and *Faecalibacterium* spp Fourfold decrease in methanogens
Saulnier et al. 2011	Fecal samples 22 pediatric IBS and 22 healthy controls 16S rRNA gene sequencing	Higher levels of Gammaproteobacteria in IBS, including higher *Haemophilus parainfluenzae* Novel Ruminococcus-like microbe associated with IBS
Carroll et al. [30]	Fecal samples 23 D-IBS and 23 healthy controls 16S rRNA gene sequencing	Reduced microbial richness in D-IBS Increased levels of *Enterobacteriaceae* in D-IBS Decreased levels of *Fecalibacterium* genera in D-IBS
Jeffery et al. [31]	Fecal samples 37 IBS (varied subtypes) and 20 healthy controls 16S rRNA gene sequencing	Lower microbial diversity in IBS Wide-ranging microbial changes in a subset of IBS ($N=22$) including increased Firmicutes and decreased Bacteroidetes among other findings
Ng et al. [32]	Rectal biopsies 10 IBS and 10 healthy controls 16S rRNA gene sequencing	Lower microbial diversity in IBS at genus but not OTU level Increased Bacteroidetes and Synergistetes in IBS Decreased Actinobacteria and Cyanobacteria in IBS
Rangel et al. [80]	Fecal samples and mucosal biopsies 35 IBS and 16 healthy controls Phylogenetic microarray	Lower Clostridiales in mucosal samples in IBS Many differences in IBS in fecal samples Notable findings including increases in Actinobacteria, Bacilli, several Clostridium clusters and Proteobacteria and a decrease in Bacteroidetes
Giamarellos-Bourboulis et al. [33]	Duodenal aspirates 74 IBS, 163 non-healthy non-IBS, and 21 healthy for qPCR 5 IBS and 5 healthy for 16S rRNA gene sequencing	Lower microbial diversity in IBS Increased *Escherichia/Shigella* and *Aeromonas* in IBS Decreased *Acinetobacter*, *Citrobacter* and *Microvirgula* in IBS
Tap et al. [38]	Fecal samples and mucosal biopsies Cohort 1: 110 IBS, 39 healthy controls Cohort 2: 29 IBS, 17 healthy controls 16S rRNA gene sequencing	Using classic approaches, no differences between IBS and healthy Computational statistics identified a microbial signature in severe IBS including methanogens and enriched by Clostridiales or Prevotella
Maharshak et al. [34]	Fecal samples and mucosal biopsies 23 D-IBS and 24 healthy subjects 16S rRNA gene sequencing	Decreased richness in IBS fecal samples only *Faecalibacterium* lower in D-IBS *Dorea* higher in D-IBS

[a]*DGGE* denaturing gradient gel electrophoresis

and resultant bacterial translocation to the circulation [53], which in turn leads to immune responses and inflammation. Interestingly, this increase in serum anti-flagellin antibodies correlated with patient anxiety scores [53], underscoring the central link between gut and brain. The reductions in bifidobacteria identified in some IBS studies [35, 36] have also been associated with impaired gut barrier function (possibly mediated through TLRs [40, 41] and/or tight junction proteins). Altered signaling by muscle-residing macrophages and secretion of cytokines, both of which may be influenced by the gut microbiota, have also been suggested to affect inflammatory responses and gut motility, possibly via effects on the interstitial cells of Cajal [54] that again are mediated by TLR signaling [55]. Lastly, serotonin (produced by intestinal enterochromaffin cells) and histamine (produced by mast cells in the mucosa) have been shown to affect inflammation and intestinal barrier integrity [56], and serotonin has also been implicated in visceral hypersensitivity. Gut microbiota appear to modulate serotonin production [57], suggesting another potential mechanism by which gut microbes may affect the gut–brain axis and potentially contribute to IBS symptoms.

Recently, it has become apparent that beyond their interaction with the gut, microbes can influence the brains of their hosts including links to psychological symptoms [58]. For example, colonization of germ-free mice with microbiota from IBS-D patients with anxiety resulted in anxiety-like behavior in those mice but not in mice colonized with microbiota from IBS-D patients without anxiety or with healthy controls [59]. In a recent human study, changes in the microbiome of IBS patients appeared to determine patterns of brain activation [60]. These findings help to integrate the seemingly disparate brain–gut axis and microbial theories of IBS.

Treating the Microbiome in IBS

Given the mounting evidence that microbes have a role in IBS, research has examined many avenues of microbial manipulation including antibiotics, probiotics, and dietary changes.

Antibiotics

The growing role of the microbiome in IBS became the basis for trials using antibiotic approaches to treat IBS. Most studies have used poorly absorbed antibiotics, neomycin or rifaximin in particular, to elicit this effect. Another study showed that norfloxacin was successful in relieving IBS symptoms, including small intestinal bacterial overgrowth [61]. In some ways, the success of antibiotics to treat IBS may represent the strongest argument for the role of bacteria in IBS.

Neomycin was one of the first antibiotics to be studied systematically for IBS. In a randomized double-blind placebo-controlled trial of 111 IBS patients fulfilling standard diagnostic criteria comparing neomycin to placebo, neomycin resulted in a 35% improvement in composite scores of IBS symptoms, compared with only 11% for placebo ($p < 0.05$) [62]. Although neomycin alone was somewhat effective in treating IBS, it is used less often due to side effects.

Rifaximin is a non-systemic antibiotic for which a number of mechanisms of action have been proposed, including potential anti-inflammatory actions, and is the most comprehensively studied antibiotic explored in the treatment of IBS-D. In two identically designed phase III trials, a single 2-week treatment with rifaximin 550 mg three times daily in patients with non-constipated IBS resulted in significantly more patients reporting adequate relief of IBS ($p = 0.01$) and bloating ($p = 0.005$) [63]. Improvement in symptoms persisted for up to 10 weeks following cessation of treatment [63]. In a more recent phase III trial to assess the safety and efficacy of repeat rifaximin treatment, 692 IBS-D patients who initially responded to rifaximin and then relapsed were randomized to double-blind rifaximin or placebo for 14 days. More patients were found to respond to retreatment with rifaximin than placebo (38.1% vs. 31.5%) [64].

A meta-analysis of clinical trials found rifaximin to be more efficacious than placebo for global IBS symptom improvement (OR = 1.57; 95% CI = 1.22, 2.01; therapeutic gain = 9.8%; number needed to treat (NNT = 10.2), with mild heterogeneity ($p = 0.25$, $I(2) = 26\%$) [65]. Importantly, rifaximin appears to have an acceptable side-effect profile with no difference in overall adverse events between the antibiotic and placebo groups. While the mechanism of rifaximin is not entirely determined, a rodent model revealed that rifaximin reduces bacterial levels in the small intestine, particularly the duodenum, but has lesser and more transient effects on colonic microbes, with stool coliform counts recovering within 3 days of cessation of treatment [66]. Due to its safety, rifaximin was approved by the FDA for the treatment of IBS-D.

Probiotics

Probiotics are widely available and may benefit patients with IBS through mechanisms that include modifying gut bacterial communities, mucosal immune function, mucosal barrier function, function of neuroendocrine cells, and fermentation [67]. Though clinical trials have evaluated the efficacy of probiotics in IBS patients, most suffer from serious methodological flaws. A recent meta-analysis that included

15 controlled trials concluded that probiotics reduce pain and symptom severity scores with a relative risk ratio for adequate improvement of IBS of 2.14 (95% CI: 1.08–4.26; $p=0.03$) [68]. Despite this observed improvement, the optimal strain, dose, formulation, and duration of therapy have not yet been determined.

In probably the most notable study using probiotics to treat IBS, *Bifidobacter infantis* 35624 led to significant improvements in abdominal pain/discomfort, bloating/distention, and/or bowel movement difficulty compared with placebo ($p<0.05$) in a randomized, blinded placebo-controlled trial conducted in IBS patients [69]. Few studies have evaluated the effects of probiotics specifically in subtypes of IBS, although a recent placebo-controlled trial evaluated a probiotic combination of three lactobacilli, three bifidobacteria, and *Streptococcus thermophiles* for 8 weeks in 50 patients with IBS-D. A significantly greater percentage of patients receiving the probiotic combination reported adequate relief of IBS compared to placebo (48% vs. 12%, $p=0.01$ reporting adequate relief for > 50% of weeks). Stool consistency also improved significantly with probiotics versus placebo [70].

Effects of Diets for IBS on the Microbiome

The low-FODMAP (fermentable oligo-, di-, and monosaccharides and polyols) diet has gained the most attention in recent years in part on the basis that it restricts consumption of food that promotes microbial fermentation in the gut. The main dietary sources of FODMAPs include dairy, wheat and other grains, many fruits and vegetables, and artificial sweeteners. Accumulating evidence from retrospective and prospective controlled trials suggests dietary FODMAP restriction is associated with reduced fermentation and significant symptom improvement in a subset of IBS sufferers [71]. Restriction of both fructose and fructans appears necessary to achieve the full clinical benefits [72]. In a randomized sham-controlled single-blind crossover trial among IBS patients who had not previously tried dietary manipulation, participants reported a significant reduction in overall gastrointestinal symptom scores compared to those on a standard Australian diet (22.8 vs., 44.9; range 0–100, $p<0.001$) [71]. Patients of all IBS subtypes had greater satisfaction with stool consistency while on the low-FODMAP diet, but IBS-D ($n=10$) was the only subtype with improvement in altered fecal frequency [71]. A recent meta-analysis that included six clinical trials found that IBS patients administered a low-FODMAP diet had significant reduction in abdominal pain, bloating, and diarrhea [73]. Long-term follow-up (i.e., > 4 weeks) is lacking.

One challenge with the low-FODMAP diet is long-term use. Response to full FODMAP restriction is usually assessed after 4–6 weeks. Responders then engage in a structured reintroduction of FODMAP-containing foods, which allows the individual to tailor their diets. The complexity of the low-FODMAP diet and the need for a structured food reintroduction phase emphasize the critical role of a properly trained dietician in the IBS care team [74]. More importantly, a recent study indicated that a low-FODMAP diet can reduce stool microbiome diversity [75], a finding usually attributed to an "unhealthy" microbiome. Thus, long-term treatment with of low FODMAP requires further study.

Fecal Microbiota Transplantation

Fecal transplantation has been an exciting area of therapeutics, with most benefit seen in recurring *C. difficile* colitis. A recent Norwegian study found that when stool from healthy individuals was transplanted into IBS-D patients during colonoscopy, clinically meaningful improvement in symptoms (defined as a decrease in the IBS-SSS score of > 75 points) occurred in 65% (36 out 75) of patients at 3 months compared with 43% (12 out 28) of patients receiving their own stool. Patients had better results if they received frozen rather than fresh fecal microbiota transplantation [76]. However, another recent study found that while fecal transplantation did alter the gut microbiome in IBS subjects, those receiving placebo reported greater symptom relief than those receiving fecal transplantation [77]. The level of current interest in this subject is evidenced by three recently presented abstracts. On balance, results are not promising, but these data await scrutiny after peer-reviewed publication. These variable results illustrate that further data are needed before considering this approach in clinical practice.

Conclusions

There is ever-growing evidence supporting the role of microbes in the pathophysiology of IBS (Table 3). It is clear from an immense body of literature that exposure to a pathogen can be an important initiating event in the development of IBS, leading to a series of downstream events that may culminate in a change in gut colonization in IBS patients (Fig. 1). These data form the basis of a new microbial hypothesis in the pathogenesis of IBS. To date, antibiotics and diet have been first-generation attempts to correct microbial perturbations and provide relief from IBS symptoms. The evolving story of the microbiome has opened up the potential for new treatments for IBS, which target the underlying cause rather than focusing only on symptom remediation. The hope is that the future of IBS research will reduce suffering, cut costs, and avoid unnecessary testing. In addition, further research is needed to explore potential means of preventing IBS. While these include protecting

Table 3 Evidence supporting a role for the microbiome in IBS

Category	Evidence
Epidemiology	
	Meta-analyses support that IBS can be precipitated by acute gastroenteritis
Diagnostics	
	Breath test abnormalities more common in IBS suggesting SIBO
	Duodenal culture demonstrates excess coliforms suggesting SIBO
	Stool microbial analyses demonstrate differences from healthy stool
	Serum antibodies to AGE toxin higher in IBS than IBD
	Some microbiome patterns associated with visceral hyperalgesia
	M. smithii (methane production) linked to constipation-predominant IBS
	Visceral hypersensitivity can be transplanted
Diet	
	Restricting fermentables in IBS appears to reduce symptoms
Antibiotics	
	Antibiotics improve symptoms in a subset of IBS with lasting effects
Probiotics	
	Some probiotics show benefits in IBS

IBS irritable bowel syndrome, *IBD* inflammatory bowel disease, *AGE* acute gastroenteritis, *SIBO* small intestinal bacterial overgrowth

against acute gastroenteritis through good hygiene, using precautions when traveling, and facilitating good water, sanitation and hygiene practices even after natural disasters, also important is identifying ways to prevent the progression to IBS, including chemoprophylaxis possibly in combination with screening for additional risk factors such as predictive cytokine and antibody panels. This review supports the concept that IBS is, at least in some patients, a microbiome-associated condition with promising therapies in the future based on a growing understanding of the disorder.

Key Messages

- Post-infectious IBS following acute gastroenteritis is triggered by the development of antibodies to the bacterial toxin CdtB which, through molecular mimicry, leads to the development of autoimmunity to the host protein vinculin.
- Anti-CdtB and anti-vinculin antibodies are useful in diagnosing IBS-D and distinguishing it from other causes of diarrhea such as IBD and celiac disease.
- The gut microbiome is altered in IBS subjects. Specific findings include lower levels of *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii* in IBS.
- Small intestinal bacterial overgrowth (SIBO) is associated with IBS-D, whereas increased levels of methanogenic archaea, specifically *Methanobrevibacter smithii*, are associated with IBS-C.
- Alterations in the gut microbiome may lead to impaired gut barrier function, which in turn may affect the brain–gut axis and potentially contribute to IBS symptoms.
- A low-FODMAP diet may result in improvements in abdominal pain, bloating, and diarrhea in IBS-D patients, but longer-term follow-up studies are needed to determine the effects on gut microbiome composition and diversity.

Compliance with Ethical Standards

Conflict of interest MP is a consultant for and has received grant support from Salix Pharmaceuticals. MP also consults for US Medical and Shire. MP has equity in and consults for Gemelli Biotech, Naia Pharmaceuticals, and Synthetic Biologics. Cedars-Sinai has licensing agreements with Bausch Health, Naia Pharmaceuticals, Synthetic Biologics and Gemelli Biotech. AL has served on the advisory boards for Allergen, Salix Pharmaceuticals, Valeant Pharmaceuticals, Alkermes, Arena, Aoen Biopharma, Takeda, Bioamerica and Ironwood Pharmaceuticals.

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