Gut Microbiota-Based Therapies for Irritable Bowel Syndrome

Emily K. Stern, MD1 and Darren M. Brenner, MD1

Irritable bowel syndrome (IBS) is a common, heterogeneous disorder characterized by abdominal pain associated with changes in bowel habits. The pathogenesis of IBS is multifactorial and may relate to alterations in the gut microbiota, changes in visceral sensation and motility, and genetic and environmental factors. Administration of systemic antibiotics may increase the risk of IBS by altering gastrointestinal homeostasis. Therapeutic interventions for IBS with diarrhea that are thought to target alterations in the gut microbiota include the nonsystemic antibiotic rifaximin, the medical food serum-derived bovine immunoglobulin, prebiotics, probiotics, and dietary modification. SYN-010 is a modified-release statin formulation that reduces methane production by Methanobrevibacter smithii and is currently in development for the treatment of patients with constipation-predominant IBS. Use of these interventions in the management of patients with IBS may function to restore a healthy gut microbiota and ameliorate symptoms of IBS.

Clinical and Translational Gastroenterology (2018) 9, e134; doi:10.1038/ctg.2018.2; published online 15 February 2018

Subject Category: Functional GI Disorders

INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder characterized by recurrent abdominal pain associated with alterations in bowel habits.1,2 The global prevalence of IBS is approximately 11%, affecting more women than men, and adults younger than 50 years of age compared with older adults.1,3 In 2016, Rome IV redefined the criteria for diagnosis of IBS, to individuals experiencing abdominal pain at least 1 day per week, concurrently meeting at least two of the following three criteria: pain that is related to defecation, pain that is associated with a change in stool frequency, or pain that is associated with change in stool texture.1 Individuals with IBS are further categorized based on their predominant stool pattern: constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), mixed IBS, and unclassified IBS.1

IBS PATHOGENESIS AND HETEROGENEITY

IBS is a complex, heterogeneous disorder and its pathogenesis differs from individual to individual.5 Factors linked to IBS symptom development include history of enteric infection, modifications in the gut microbiota, immunomodulation, alterations in brain–gut processing, and changes in visceral sensation and motility.2,4–6 Neuroimmunologic signaling in response to a precipitating event at the mucosal surface stimulates communication through multiple pathways that can lead to the development of visceral hypersensitivity and alterations in stool frequency and form.5 However, the factors involved and their relative contributions to the development, frequency, and severity of symptoms differ between individuals.2,7–11 Despite decades of research, the specific mechanistic pathways involved in the development of IBS are only beginning to be elucidated. An association with small intestinal bacterial overgrowth (SIBO) has been observed in subpopulations of patients with IBS5,12–16 although a causal relationship between SIBO and IBS remains to be established.17 Nonetheless, changes in the gut microbiota are thought to trigger alterations in gut permeability, motility, visceral perception, and food processing, ultimately resulting in IBS symptoms.6,18,19 The goal of the current article is to provide an overview of the role of altered GI homeostasis in IBS and present therapeutic options.

THE ROLE OF ALTERED GUT MICROBIOTA IN IBS

The term “gut microbiota” represents the totality of microbes that collectively inhabit the GI tract.20 Historically, it has been argued that the average individual contains 10 times more microbial cells than human cells,21,22 but newer data contest this hypothesis.23 In either case, several trillion microbes are found within the GI tract, and this community plays a central role in the health and function of the GI system.20 Multiple studies have demonstrated altered intestinal microbiota in patients with IBS.24 For example, compared with healthy individuals, brushings of duodenal mucosa in patients with IBS showed significantly lower Bifidobacterium catenulatum counts (P<0.001).25 Furthermore, a 2017 systematic review and meta-analysis demonstrated that patients with IBS (n = 360) had significantly less bacterial colonization of...
Lactobacillus, Bifidobacterium, and Faecalibacterium prausnitzii based on quantitative real-time PCR analysis compared with healthy individuals \((n=268; \ P<0.001, \text{ for all comparisons})\).24

Alterations in the gut microbiota are thought to be associated with changes in GI function that have been observed in patients with IBS.5,26 For example, fecal aspirates from patients with IBS applied to the colonic mucosa of mice were shown to increase intestinal permeability,27 and the administration of fecal microbiota transplants from patients with IBS to germ-free mice induced alterations in GI motility, as well as hypersensitivity to colonic distension.28,29 Furthermore, patients with IBS have increased expression of colonic toll-like receptors (TLRs), which are involved in the immune response to enteric bacteria.18 TLR-4 detects lipopolysaccharide (LPS), a component of the cell membrane of Gram-negative bacteria.30 Through intricate signaling pathways, LPS exposure can lead to increased production of proinflammatory cytokines.30 TLR-4 signaling is also important for the health and survival of GI neuronal cells,18,30 and a lack of TLR-4 signaling can delay GI motility.30 In addition, GI microbes have the potential to modulate the enteroendocrine system;31 specifically, data have suggested that indigenous microbes in healthy individuals produce metabolites that promote serotonin synthesis in the GI tract.31 Serotonin is known to play a role in GI motor and sensory functions,31 and modulation of the gut microbiota may influence serotonin-related GI functions. Overall, these studies suggest that disruptions in gut microbiota may play a causative role in the pathogenesis of IBS.21,32

The most well-documented line of evidence linking disruption of GI microbial homeostasis to the development of IBS symptoms comes from the literature on postinfectious IBS (PI-IBS), in which the reported rates of prior GI infection in patients with PI-IBS ranged between 10% and 53%.33,34 A systematic review reported that an acute GI illness increased the risk of PI-IBS by 7-fold.35 Patients who develop PI-IBS do not fully downregulate their normal inflammatory responses to a GI infection.36 These patients, therefore, have ongoing GI inflammation characterized by increased rectal mucosal epithelial lymphocytes and cytokine upregulation.36 Persistent inflammation can also cause increased intestinal permeability that leads to further immune system activation and GI inflammation.36 Furthermore, genetic studies suggest that patients who develop PI-IBS may have an innate susceptibility to an infectious trigger or to the development of ongoing GI dysfunction.37

Similarly, a prospective community-based study has shown that systemic antibiotic exposure can increase the risk of developing IBS symptoms by at least 3-fold, presumably through alterations in GI homeostasis.38 A retrospective analysis of medical records at a single institution noted that a significantly greater percentage of patients who had received a macrolide or tetracycline antibiotic during the previous year developed IBS compared with patients who did not develop IBS \((P=0.04 \text{ and } P<0.02, \text{ respectively})\).39

An alternative pathway connecting the gut microbiota and IBS has developed from studies that associated IBS with SIBO. Several studies have reported that patients with IBS have a higher prevalence of SIBO compared with healthy individuals.12,40–42 The prevalence of SIBO in patients with IBS was reported to range between 46% and 50%.42,43 Breath test results were approximately 10 times more likely to be positive in patients with IBS compared with age- and sex-matched controls,40 and culture of duodenal aspirates—considered the gold standard for SIBO determination—revealed that patients with IBS-D had higher total bacterial counts compared with healthy individuals, as well as different sets of predominant bacterial species.35,44 In addition, eradication of SIBO has been shown to correlate with improvement in IBS symptoms.42 Therefore, it is plausible that both the absolute number and types of microbes are important in maintaining gut homeostasis, and that SIBO plays a role in the pathogenesis of IBS in a subset of patients.15,44

Food represents another plausible factor in the pathogenesis of IBS. Most patients experience a triggering or exacerbation of IBS symptoms when they eat a meal.45 Foods may directly affect gut microbial composition.46 Patients with IBS consuming a diet low in fermentable oligo-, di-, mono-saccharides, and polyols (FODMAP) for 3 weeks had an increase in richness and diversity of fecal Actinobacteria species, whereas a high FODMAP diet was associated with decreased numbers of gas-consuming bacteria.46 Food can also influence intestinal motility, sensation, and neural activity,47 and the gut microbiota may have a role in some of these effects. For example, when gut microbes ingest dietary components, they can produce potential symptom-inducing metabolites.48 Fat and digested proteins can increase bile acid excretion, which leads to increased intestinal motility and colonic secretion of water and electrolytes.48–50 In the colon, bacterial fermentation of oligosaccharides into carbon dioxide and hydrogen can lead to sensations of pain and bloating, with reflex response of the diaphragm and anterior abdominal wall resulting in distension.51,52 Hydrogen can be used to form methane by anaerobic archaea, such as Methanobrevibacter smithii;48,53 and evidence suggests that methane slows GI motility and may contribute to constipation.53 In fact, excess methanogenesis has been purported as a plausible pathogenic mechanism for the development of IBS-C.52 A better understanding of these mechanisms has, and will continue, to result in new treatment modalities for this disorder.

**TREATMENT OF GUT MICROBIAL-RELATED IBS**

Rifaximin. Several IBS therapeutics have been developed that target the gut microbiota or the secondary consequences of alterations in the gut microbiota (Table 1).14,53–68 One of the most well-studied treatments for IBS is the non-absorbable antibiotic rifaximin. Rifaximin is currently available in 47 countries; it has been available in Italy since 1987 and in the United States since 2004. Rifaximin was approved by the US Food and Drug Administration in 2015 for the treatment of adults with IBS-D.69 Although the exact mechanism of action in IBS-D is unclear, rifaximin is a bile-soluble molecule with bactericidal properties that affect aerobic and anaerobic organisms inhabiting the GI tract.59,64 Evidence also suggests that rifaximin contains inherent properties capable of mediating inflammatory responses to GI microbes.62 In two phase 3, identically designed, randomized, double-blind,
placebo-controlled trials (Targeted, nonsystemic Antibiotic Rifaximin Gut-selective Evaluation of Treatment for IBS-D (TARGET) 1 and TARGET 2), patients with IBS without constipation received a 2-week course of rifaximin 550 mg three times daily and subsequently entered a 10-week follow-up period. A significantly greater percentage of patients receiving rifaximin reported adequate relief of global IBS symptoms for at least two of the first 4 weeks after treatment compared with placebo (40.7% vs. 31.7%, respectively; P < 0.001 (data pooled)). Patients treated with rifaximin also reported significant improvements in outcomes for bloating, abdominal pain, and stool consistency versus placebo for at least two of the first 4 weeks after treatment (P < 0.003 for all outcomes). Rifaximin was well tolerated and comparable to placebo, with the most common adverse events with rifaximin vs. placebo being headache (6.1% vs. 6.6%), upper respiratory tract infection (5.6% vs. 6.2%), and abdominal pain (4.6% vs. 5.5%). Overall symptom improvement persisted for at least 10 weeks post treatment, suggesting that a course of rifaximin may “reset” the gut microbiota and restore a healthy microbe community. However, the percentage of patients with adequate relief decreased in both groups during the 10-week follow-up period, although the percentage of patients with adequate relief was significantly greater with rifaximin compared with placebo during this period (P = 0.001).

In a repeat treatment trial (TARGET 3) that examined the efficacy and safety of up to 3 courses of rifaximin treatment, 692 (64.4%) of 1,074 patients with initial response to a 2-week course of rifaximin experienced recurrence within 18 weeks post treatment. Of these patients, 636 were randomly assigned in a double-blind manner to repeat treatment with rifaximin 550 mg or placebo 3 times daily for 2 weeks. With repeat treatment, a significantly larger percentage of individuals responded to rifaximin compared with placebo (38.1% vs. 31.5%, respectively; P = 0.03). Rifaximin was well tolerated during the trial. The most common adverse events during double-blind repeat treatment with rifaximin vs. placebo were nausea (3.7% vs. 2.3%), upper respiratory tract infection (3.7% vs. 2.6), and urinary tract infection (3.4% vs. 4.9). Importantly, drug-related adverse events were lower in the rifaximin group than the placebo group (1.8% vs. 2.6%). Furthermore, after exposure of up to three 2-week courses or rifaximin during the TARGET 3 trial, there was no evidence of bacterial antibiotic resistance. No cases of *Clostridium difficile* were observed during rifaximin treatment in a phase 2b study or the three TARGET trials, with the exception of 1 patient in TARGET 3. This patient developed *C. difficile* colitis 37 days after rifaximin repeat treatment and had received cefdinir for 10 days for a urinary tract infection immediately before the adverse event.

Rifaximin has also been studied in a cohort of patients with IBS with documented concomitant SIBO. In a study of 106 individuals with IBS and a positive lactulose hydrogen breath test, patients treated with a 2-week course of rifaximin had significant improvements from baseline in IBS symptoms of abdominal pain, bloating, diarrhea, flatulence, and overall well-being at week 4 (2 weeks posttreatment; P < 0.05 for all comparisons). Of 64 patients who underwent a repeat lactulose hydrogen breath test, 86% had a negative result, suggesting that improvement in IBS symptoms may be mediated by the eradication of SIBO.

Rifaximin may also be beneficial for treating patients with IBS-C. As discussed previously, IBS-C symptoms have been linked to elevations in GI methane levels. A retrospective study reported that neomycin 500 mg twice daily plus rifaximin 400 mg three times daily for 10 days eliminated methane levels in 87% of patients and improved overall clinical results.
Gut microbiota-based therapies for IBS
Stern and Brenner

Symptoms in patients with IBS.75 A small double-blind, randomized, placebo-controlled trial subsequently demonstrated that neomycin plus rifaximin was superior to neomycin alone in improving IBS-C symptoms.61 In this trial, 32 patients were randomly assigned to 14 days of treatment with either neomycin 500 mg twice daily plus placebo 3 times daily or neomycin 500 mg twice daily plus rifaximin 550 mg 3 times daily.61 Patients in the neomycin plus rifaximin group noted significant improvements compared with the neomycin plus placebo group in constipation, straining, and bloating.61 In addition, patients treated with neomycin plus rifaximin, who had lower methane levels post treatment had less severe constipation than those treated with combination therapy for whom high methane levels persisted post treatment (P = 0.02).61

SYN-010. SYN-010 is a nonabsorbable derivative of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor lovastatin lactone; this modified-release statin formulation is thought to decrease methane production by blocking cell membrane biosynthesis of M. smithii, a predominant methane producer in the GI tract.53,66,76 In a phase 2 study, 62 patients with IBS-C and elevated breath methane levels were treated with 4 weeks of SYN-010 21 mg, SYN-010 42 mg, or placebo once daily.76 After 1 week, only the higher dose of SYN-010 significantly reduced methane levels from baseline (P = 0.047; primary endpoint). After 4 weeks of treatment, patients in both active treatment groups had significantly decreased breath methane levels from baseline, whereas patients in the placebo group did not (P = 0.03 for 21 mg dose, P = 0.009 for 42 mg dose).76 In addition, after 4 weeks of treatment, patients who received the 42 mg dose reported significant improvements in abdominal pain (P = 0.08) and patients treated with the 21 mg dose reported significant improvements in stool frequency (P = 0.02).76 This study demonstrated that SYN-010 reduced intestinal methane production with a longer duration of treatment (4 weeks) and showed improvement in some clinical parameters, despite not being powered for these outcomes.76

Serum-derived bovine immunoglobulin. Other agents that impact GI homeostasis may also improve IBS symptoms. Serum-derived bovine immunoglobulin (SBI), an IgG preparation, has been approved by the US Food and Drug Administration as a prescription medical food for patients with IBS-D.77 SBI has also been studied in other disorders such as HIV enteropathy and IBD.65,78 SBI may, theoretically, help maintain a normal gut microbiota and decrease intestinal permeability,65 although there is no evidence that SBI alters the gut microbial community structure. Evidence for SBI use in IBS-D is still limited to preclinical and anecdotal (e.g., case report) data and a small underpowered clinical trial.65,79,80

Prebiotics, probiotics, and synbiotics. Prebiotics, probiotics, and synbiotics may relieve IBS symptoms by modulation of gut microbial composition and activity. Prebiotics—non-digestible food ingredients promoting proliferation of healthy GI bacteria—have been shown in preclinical studies to exert anti-inflammatory effects, inhibit adherence of pathogens to the GI epithelium, and stimulate enhancement of the intestinal mucosal layer.68 In a randomized, patient-blinded, placebo-controlled clinical study of 44 adults with IBS, oral treatment with a trans-galactooligosaccharide mixture was associated with significant improvements in flatulence, bloating, an IBS-specific questionnaire, and a subjective global assessment compared with placebo (P < 0.05 for each).81 The treatment also significantly increased the proportions of fecal Bifidobacterium compared with placebo. Another randomized, double-blind, placebo-controlled study (n = 105) examined the influence of a short-chain fructo-oligosaccharide complex on digestive symptoms and quality of life, using questionnaires.62 Those receiving short-chain fructo-oligosaccharide experienced significantly greater reductions in digestive symptom intensity (P = 0.03) and greater improvement in performance of daily activities (P = 0.02) than those receiving placebo. Although short-chain fructo-oligosaccharide has been shown to enhance growth of fecal Bifidobacteria, changes in gut microbiota were not assessed in this study.

Probiotics are living microorganisms (e.g., bacteria) ingested in the form of foodstuffs and supplements.54 Several studies have suggested that daily use of probiotics may improve IBS symptoms.54,83 Between-study comparisons, as well as meta-analyses, are limited, because studies often use different combinations of bacterial strains.54 Although the exact mechanism of action by which probiotics modulate the gut microbiota is unclear, probiotics are hypothesized to impede colonization of pathogenic bacteria; secrete bacteriocids and chemical defenses that degrade bacterial toxins, activate and augment the enteric nervous system; and regulate the production of multiple vitamins and micronutrients, such as folate and vitamin K.55 Currently, the best evidence for probiotic use in patients with IBS is the success with strains of the Bifidobacterium genus that has been reported in the literature.21,54 A randomized, placebo-controlled study of 362 women with IBS of any subtype who were given a 4-week course of Bifidobacterium infantis 35624 at a dose of 1 × 10^9 colony-forming units (CFU ml^-1) had significant improvements in global symptoms at the end of treatment (P = 0.01).84 Patients who received B. infantis 35624 1 × 10^9 CFU ml^-1 also reported significant improvements in subscores of abdominal pain, bloating, bowel dysfunction, incomplete evacuation, and straining, compared with placebo (P < 0.05 for all comparisons).84 A randomized, double-blind, active-controlled trial of patients with IBS-C who received Bifidobacterium animalis DN-173 010 showed significant improvements in the scores for health-related discomfort (P < 0.005) and bloating (P = 0.03) at week 3. In general, the American College of Gastroenterology concluded that, as a whole, probiotics facilitate global improvement of IBS symptoms, bloating, and flatulence, but this recommendation was considered weak and based on a low quality of evidence.85

Synbiotics, combinations of probiotics and prebiotics, are still in a fledgling stage with respect to evaluations of their ability to improve IBS symptoms. In a randomized, double-blind, placebo-controlled study of patients with IBS (n = 25), a synbiotic (a complex of 29 micro-organisms plus a prebiotic made up mostly of leonardite, a complex of high-and low-molecular weight humic substances, added to enhance
proliferation of the micro-organisms) was associated with significant reductions in general ill feelings/nausea \( (P=0.04) \), indigestion/flatus/naira (\( P=0.008 \)) and colitis (\( P=0.003 \)) compared with placebo.\(^{67}\)

**Dietary modification.** Dietary modification to manage IBS symptoms has become increasingly popular, as 50–75% of patients believe that there is an association between the meals they consume and their symptoms.\(^{1,45}\) As discussed previously, the breakdown products of food consumption directly affect GI motility, GI permeability, and immune regulation.\(^{45} \) Thus, a diet restricting foods that induce these changes, or a diet that alters the gut microbiota in a positive manner, would be beneficial to manage IBS symptoms.\(^{45} \) The most well-studied dietary strategy in IBS is the low FODMAP diet.\(^{45} \) FODMAPs are short-chain, highly fermentable carbohydrates that are poorly absorbed and rapidly fermented by GI bacteria into gases such as methane and hydrogen.\(^{45,67} \) They also increase intraluminal fluid, which may cause GI distension and stimulate peristalsis.\(^{67} \) A 2016 meta-analysis reported that significant improvement in symptom severity scores was observed for an IBS population on a low FODMAP diet in randomized controlled trials (6 trials) and nonrandomized interventional trials (16 trials).\(^{88} \) Compared with other dietary modifications, however, FODMAPs have led to conflicting results. In a study by Bohn et al.,\(^{89} \) a diet low in FODMAPs was not found to be superior in reducing IBS symptom severity compared with traditional dietary advice. In the first randomized controlled IBS-D trial that compared the low FODMAP diet to a diet consistent with the modified National Institute for Health and Care Excellence guidelines from the United Kingdom, no significant difference in adequate relief of overall symptoms during \( \geq 50\% \) of the final 2 weeks of the 4-week assessment period was observed between the low FODMAP diet (52.3%) and guideline (41.0%); \( P=0.3 \) groups.\(^{67} \) However, unlike the guideline group, patients consuming a low FODMAP diet reported significantly greater improvements from baseline in abdominal pain, bloating, stool consistency, and urgency during each of the 4 weeks of dietary modification \( (P<0.05 \) for all comparisons).\(^{67} \)

It is apparent to practitioners and patients alike that a low FODMAP diet is restrictive, difficult to maintain, and potentially unsafe in the long term.\(^{67} \) Concerns with long-term implementation of a low FODMAP diet include nutritional inadequacy, disordered eating, and alterations in the gut microbiota.\(^{90} \) Presence of *Bifidobacteria* species—a common genus of commensal organisms in the GI tract that has been linked negatively to pain and abdominal symptoms in patients with IBS—is reduced in the GI tract of patients with IBS.\(^{25,90,91} \) These organisms can be further reduced by the consumption of a very low FODMAP diet.\(^{91} \) This further supports the important interplay in the GI tract among food, bacteria, and IBS symptoms. Fructans and galacto-oligosaccharides have prebiotic properties, and the reduction of these foodstuffs may also reduce beneficial bacterial colonies in the GI tract.\(^{90} \) Finally, FODMAP removal reduces concentrations of bacteria responsible for producing the beneficial short-chain fatty acid butyrate.\(^{15,90} \) Thus, in the experience of these authors, reintroduction of specific FODMAPs—even in individuals experiencing significant symptom improvements—is necessary. However, the process of how to do this has yet to be elucidated and further studies accounting for the roles of certain FODMAP-containing classes of foods and their effects on IBS symptoms and the gut microbiota are necessary.

**CONCLUSIONS**

IBS is a complex disease with a high prevalence.\(^{1} \) The pathogenesis of the disease is likely multifactorial.\(^{2} \) Available data suggest that gut microbiota contribute to disease pathogenesis and expression in multiple ways, including effects on GI immune system activation and inflammation, membrane permeability, intestinal motility, gut-brain communication, and gas production. Treatment options aimed at restoring a healthy GI tract microbial environment are available or are being evaluated. Further research on the potential benefits of available and treatments in development, including an understanding of their effects on the pathophysiological mechanisms of IBS, is warranted.

**CONFLICT OF INTEREST**

Guarantor of the article: Darren M. Brenner, MD.

Specific author contributions: Dr. Stern wrote the first draft of the manuscript. Dr. Brenner revised and edited the first and all subsequent drafts of the manuscript. Both authors equally planned the review, collected and interpreted the data, and have approved the final draft submitted.

Potential competing interests: Dr. Stern has no conflicts to disclose. Dr. Brenner has served as a consultant/advisor and is on the speakers’ bureau for Allergan, AstraZeneca, Daiichi Sankyo, GI Health Foundation, Ironwood, Salix, and Synergy Pharmaceuticals.

**Acknowledgments.** Technical editorial and medical writing assistance were provided by Mary Beth Moncrieff, PhD, and Sophie Bolick, PhD, for Synchrony Medical Communications, LLC, West Chester, PA, USA, under the direction of the authors. Funding for this support was provided by Salix Pharmaceuticals, Bridgewater, NJ, USA. No remuneration for the development of the article was received.

1. Lacy BE, Mearin F, Chang L et al. Bowel disorders. Gastroenterology 2016; 150: 1393–1407.
2. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. JAMA 2015; 313: 949–958.
3. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2010; 12: 712–721.
4. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. N Engl J Med 2017; 376: 2566–2578.
5. Ghoshal UC, Shukla R, Ghoshal U et al. The gut microbiota and irritable bowel syndrome: friend or foe? Int J Inflam 2012; 2012: 151085.
6. Konig J, Wells J, Cani PD et al. Human intestinal barrier function in health and disease. Clin Transl Gastroenterol 2016; 7: e196.
7. Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 2012; 303: G775–G785.
8. Top J, Denien M, Toriblom H et al. Identification of an intestinal microbiota signature associated with severity of irritable bowel syndrome. Gastroenterology 2017; 153: 111–123 e118.
9. Simmen M, Toriblom H, Palsson OS et al. Visceral hypersensitivity is associated with GI symptom severity in functional GI disorders: consistent findings from five different patient cohorts. Gut 2018; 67: 255–262.
10. Bennett SM, Poletier A, Toriblom H et al. Global cytokine profiles and association with clinical characteristics in patients with irritable bowel syndrome. Am J Gastroenterol 2016; 111: 1165–1176.
11. Palsson OS, Baggah JS, Turner MJ et al. IBS patients show frequent fluctuations between loose/watery and hard/lumpy stools: implications for treatment. Am J Gastroenterol 2012; 107: 286–295.
Clinical and Translational Gastroenterology

12. Giamarellos-Bourboulis EJ, Pylyeris E, Barbatzas C et al. Small intestinal bacterial overgrowth is associated with irritable bowel syndrome and is independent of proton pump inhibitor usage. BMC Gastroenterol 2016; 16: 67.

13. Shimura S, Ishimura N, Mikami H et al. Small intestinal bacterial overgrowth in patients with refractory functional gastrointestinal disorders. J Neurogastroenterol Motil 2016; 22: 60–68.

14. Ghoshal UC, Srivastava D. Irritable bowel syndrome and small intestinal bacterial overgrowth: meaningful association or unnecessary hype. World J Gastroenterol 2014; 20: 2482–2491.

15. Pylyeris E, Giamarellos-Bourboulis EJ, Tzviras D et al. The prevalence of overgrowth by aerobic bacteria in the small intestine by small bowel culture: relationship with irritable bowel syndrome. Dig Dis Sci 2012; 57: 1321–1329.

16. Sachdeva S, Rawat AK, Reddy RS et al. Small intestinal bacterial overgrowth (SIBO) in irritable bowel syndrome: frequency and predictors. J Gastroenterol Hepatol 2011; 26 (Suppl 3): 135–138.

17. Jia J, SM. Questioning the bacterial overgrowth hypothesis of irritable bowel syndrome: an epidemiological and evolutionary perspective. Clin Gastroenterol Hepatol 2011; 9: 461–468.

18. Ringel Y, Ringel-Kulka T. The intestinal microbiota and irritable bowel syndrome. J Clin Gastroenterol 2015; 49 (Suppl 1): S56–S59.

19. Guatino MP, Cicala M, Pulvigrani L et al. Gastrointestinal neuromuscular apparatus: an update. Reviewing a systemic review and meta-analysis. Dig Liver Dis 2017; 49: 331–337.

20. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med 2016; 375: 2369–2379.

21. Simrén M, Barbara G, Flint HJ et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut 2013; 62: 159–176.

22. Szezky P, Russell AC, Antunes LC et al. Gut microbiota in health and disease. Physiol Rev 2010; 90: 895–904.

23. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell 2016; 164: 337–340.

24. Liu HN, Hu H, Chen YZ et al. Altered molecular signature of intestinal microbiota in irritable bowel syndrome patients compared with healthy controls: a systematic review and meta-analysis. Dig Liver Dis 2017; 49: 331–337.

25. Kerckhoffs AP, Samsom M, van der Rest ME. Small intestinal bacterial overgrowth (SIBO) in patients without constipation: a colonic lumenal factor impairing colonic permeability and sensitivity. J Clin Gastroenterol 2013; 47: 197–212.

26. Kerckhoffs AP, Samsom M, van der Rest ME. Small intestinal bacterial overgrowth (SIBO) in irritable bowel syndrome patients compared with healthy controls: a systematic review and meta-analysis. J Gastroenterol Hepatol 2011; 26 (Suppl 3): 135–138.

27. Jia J, SM. Questioning the bacterial overgrowth hypothesis of irritable bowel syndrome: an epidemiological and evolutionary perspective. Clin Gastroenterol Hepatol 2011; 9: 461–468.

28. Ringel Y, Ringel-Kulka T. The intestinal microbiota and irritable bowel syndrome. J Clin Gastroenterol 2015; 49 (Suppl 1): S56–S59.

29. Guatino MP, Cicala M, Pulvigrani L et al. Gastrointestinal neuromuscular apparatus: an update. Reviewing a systemic review and meta-analysis. Dig Liver Dis 2017; 49: 331–337.

30. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med 2016; 375: 2369–2379.

31. Simrén M, Barbara G, Flint HJ et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut 2013; 62: 159–176.

32. Szezky P, Russell AC, Antunes LC et al. Gut microbiota in health and disease. Physiol Rev 2010; 90: 895–904.

33. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell 2016; 164: 337–340.

34. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med 2016; 375: 2369–2379.

35. Simrén M, Barbara G, Flint HJ et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut 2013; 62: 159–176.

36. Szezky P, Russell AC, Antunes LC et al. Gut microbiota in health and disease. Physiol Rev 2010; 90: 895–904.

37. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell 2016; 164: 337–340.
81. Silk DB, Pimentel M, Chang L et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomised, double-blind, placebo-controlled trials. Aliment Pharmacol Ther 2014; 39: 1161–1168.

76. Gottlieb K, Wacher V, Sliman J et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome with a positive lactulose hydrogen breath test improves symptoms for at least 3 months. Am J Gastroenterol 2012; 107: 1561–1569.

75. Low K, Hwang L, Hua J et al. A combination of rifaximin and neomycin is most effective in treating irritable bowel syndrome patients with methane on lactulose breath test. J Clin Gastroenterol 2010; 44: 547–550.

80. Wilson D, Evans M, Weaver E et al. Evaluation of a trans-galactooligosaccharide prebiotic in faecal microbiota and symptoms in irritable bowel syndrome. Gut 2006; 55: 1407–1416.

79. Shafran I, Burgunder P, Wei D et al. Management of inflammatory bowel disease with oral serum-derived bovine immunoglobulin. Therap Adv Gastroenterol 2015; 8: 331–339.

78. Shafran I, Burgunder P, Wei D et al. Management of inflammatory bowel disease with oral serum-derived bovine immunoglobulin. Therap Adv Gastroenterol 2015; 8: 331–339.

77. ENTERAGAM (serum-derived bovine immunoglobulin/protein isolate, SBI) (package insert). Entera Health, Inc.: Ankeny, Iowa; 2015.

86. Ford AC, Moayyedi P, Lacy BE et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol 2014; 109: S2–S26.

85. Guyonnet D, Chassany O, Ducrotte P et al. Effect of a fermented milk containing Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006; 101: 1561–1590.

84. Whorwell PJ, Altringer L, Morel J et al. Effect of a fermented milk containing Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006; 101: 1561–1590.

83. Ford AC, Quigley EMM, Lacy BE et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Eur J Nutr 2016; 55: 897–906.

82. Paineau D, Payen F, Panserieu S et al. A new therapeutic option for irritable bowel syndrome: serum-derived bovine immunoglobulin. World J Gastroenterol 2015; 21: 3301–3306.

81. Silk DB, Pimentel M, Chang L et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomised, double-blind, placebo-controlled trials. Aliment Pharmacol Ther 2014; 39: 1161–1168.

80. Wilson D, Evans M, Weaver E et al. Evaluation of serum-derived bovine immunoglobulin protein isolate in subjects with diarrhea-predominant irritable bowel syndrome. Cln Med Insights Gastroenterol 2013; 6: 49–60.

79. Shafran I, Burgunder P, Wei D et al. Management of inflammatory bowel disease with oral serum-derived bovine immunoglobulin. Therap Adv Gastroenterol 2015; 8: 331–339.

83. Ford AC, Quigley EMM, Lacy BE et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Am J Gastroenterol 2014; 109: 1547–1561.

82. Paineau D, Payen F, Panserieu S et al. A new therapeutic option for irritable bowel syndrome: serum-derived bovine immunoglobulin. World J Gastroenterol 2015; 21: 3301–3306.

78. Shafran I, Burgunder P, Wei D et al. Management of inflammatory bowel disease with oral serum-derived bovine immunoglobulin. Therap Adv Gastroenterol 2015; 8: 331–339.

86. Ford AC, Moayyedi P, Lacy BE et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol 2014; 109: S2–S26.

85. Guyonnet D, Chassany O, Ducrotte P et al. Effect of a fermented milk containing Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006; 101: 1561–1590.

84. Whorwell PJ, Altringer L, Morel J et al. Effect of a fermented milk containing Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006; 101: 1561–1590.

83. Ford AC, Quigley EMM, Lacy BE et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Am J Gastroenterol 2014; 109: 1547–1561.

82. Paineau D, Payen F, Panserieu S et al. A new therapeutic option for irritable bowel syndrome: serum-derived bovine immunoglobulin. World J Gastroenterol 2015; 21: 3301–3306.

81. Silk DB, Pimentel M, Chang L et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomised, double-blind, placebo-controlled trials. Aliment Pharmacol Ther 2014; 39: 1161–1168.

80. Wilson D, Evans M, Weaver E et al. Evaluation of serum-derived bovine immunoglobulin protein isolate in subjects with diarrhea-predominant irritable bowel syndrome. Cln Med Insights Gastroenterol 2013; 6: 49–60.

79. Shafran I, Burgunder P, Wei D et al. Management of inflammatory bowel disease with oral serum-derived bovine immunoglobulin. Therap Adv Gastroenterol 2015; 8: 331–339.

86. Ford AC, Moayyedi P, Lacy BE et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol 2014; 109: S2–S26.

85. Guyonnet D, Chassany O, Ducrotte P et al. Effect of a fermented milk containing Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006; 101: 1561–1590.

84. Whorwell PJ, Altringer L, Morel J et al. Effect of a encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006; 101: 1561–1590.

83. Ford AC, Quigley EMM, Lacy BE et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Am J Gastroenterol 2014; 109: 1547–1561.

82. Paineau D, Payen F, Panserieu S et al. A new therapeutic option for irritable bowel syndrome: serum-derived bovine immunoglobulin. World J Gastroenterol 2015; 21: 3301–3306.

81. Silk DB, Pimentel M, Chang L et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomised, double-blind, placebo-controlled trials. Aliment Pharmacol Ther 2014; 39: 1161–1168.