Irritable Bowel Syndrome: Emergence of New Diagnostic and Treatment Options

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Abstract

Background: Diagnosis and treatment options for irritable bowel syndrome (IBS) have traditionally addressed the clinical symptoms of the disease, including constipation, diarrhea, and abdominal pain. New understanding of the pathophysiology of IBS, including the potential association of small intestinal bacterial overgrowth (SIBO) with the disorder, promises to yield new diagnostic techniques and therapies to supplement symptom-based approaches.

Purpose: This article reviews symptom-based diagnostic criteria and treatment options for IBS and discusses emerging diagnostic techniques, such as breath testing. It also reviews new pharmacologic therapies, including opioids, antibiotics, and other agents currently being evaluated. Symptom-based criteria will continue to be useful in the diagnosis of IBS, but these may be augmented by new techniques such as hydrogen and methane breath testing. Further understanding of the body's physiologic response to IBS may identify diagnostically relevant biologic markers. Nontraditional therapies, such as

antibiotics (eg, rifaximin) and probiotics, may target SIBO as an underlying cause of IBS and have shown efficacy in disease management.

Conclusion: IBS treatment options will likely expand beyond mere management of clinical symptoms. Diagnostic and treatment options for IBS will continue to evolve with further understanding of the disorder, but addressing the symptoms of the disease and their relief by pharmacologic therapies will remain the goals of IBS management.

Key words: irritable bowel syndrome, IBS, breath testing, rifaximin

Introduction

Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal (GI) tract characterized by alterations in bowel function accompanied by abdominal pain and discomfort, including symptoms such as bloating and bowel urgency.[1-3] The abnormal bowel habits associated with IBS may be constipation-predominant (IBS-C) or diarrhea-predominant (IBS-D), or they might involve alternating or mixed periods of both (IBS-A).[1,2] The prevalence of IBS in North America is estimated to be 10% to 15%.[2,3] The disorder is more prevalent in females than males,[2-4] but this bias may be less pronounced than practitioners generally perceive. Although IBS is the most commonly made diagnosis by gastroenterologists,[4] the disorder often goes unrecognized or untreated, with as few as 25% of people with IBS seeking clinical care.[2] The direct and indirect annual cost of IBS in the United States is approximately $30 billion,[4] and it is a substantial source of missed work and loss of productivity.[5]

The diagnosis of IBS is primarily based on clinical symptoms and the exclusion of other conditions (eg, inflammatory bowel disease [IBD], celiac disease, colorectal cancer, lactose intolerance).[6,7] Thus, there has been a historical tendency to view IBS as a “diagnosis of exclusion” or as a hypersensitivity syndrome without explanation.[8] Although no single biologic marker exists to reliably identify patients with IBS,[6] the emergence of new diagnostic techniques offers options for clinicians while helping to elucidate the pathophysiology of this common disorder. As the understanding of IBS and diagnostic methods progress, new testing procedures will likely complement, rather than replace, existing symptom-based diagnostic criteria.

Similarly, treatment options for IBS have traditionally focused on symptomatic relief of constipation, diarrhea, and discomfort associated with the disorder,[9] but as understanding of the disease etiology progresses, new pharmacologic agents are being evaluated that may address the underlying causes of IBS. Therapies that target these underlying causes may have broad benefit for all patients with IBS, rather than merely managing disease symptoms in subgroups of patients. This review article will summarize the symptomatic

diagnostic criteria and treatment options for IBS and highlight new diagnostic methods and therapies showing promise in the management of the disorder.

Symptom-Based Diagnosis of IBS

Methodologies for diagnosing IBS have been evolving since the 1970s. Among commonly used, symptom-based criteria, the Manning criteria have been the most extensively evaluated.[6,7] The Manning criteria consist of 6 symptoms meant to differentiate IBS from other GI disorders (Table 1)[10] and are associated with a positive predictive value of 65% to 75%.[6] Building upon the Manning criteria, the Rome diagnostic criteria have been developed by expert consensus and have been periodically revised.[1,8,11] The most recent version (Rome III) is designed to improve the clinical usefulness of the criteria and describes 3 phenomena that, when coincident with the recurrence of abdominal pain or discomfort, are associated with a diagnosis of IBS (Table 1).[1] The Rome criteria represent useful advances in diagnostic consistency, but many symptoms commonly associated with IBS, including symptom worsening during menstruation,[12] fatigue and insomnia,[13] and urinary symptoms,[14,15] are not included in the diagnosis algorithm.

Clinicians may perform supplemental diagnostic tests to confirm and diagnose IBS, often by excluding disorders with similar symptomologies. Blood tests may be performed to detect anemia and other abnormalities inconsistent with IBS.[16] Diagnoses of thyroid disease may be excluded by performing thyroid function tests, including measuring levels of thyroid-stimulating hormone.[17] However, these results must be carefully considered, as thyroid function abnormalities are common in the general population,[18] and increased or decreased thyroid function may be present in patients with IBS as well.[17] Antibody testing may also be recommended to help exclude a diagnosis of celiac disease.[16,19] While symptom-based diagnostic criteria for IBS, combined with tests to exclude alternate diagnoses, will continue to have clinical usefulness, the development of additional diagnostic methods promises to assist clinicians in reliably identifying patients with IBS. These new methods, including investigation into identifying reliable biomarkers associated with IBS, are invariably connected to progress in understanding the pathophysiology and etiology of the disorder and stand to establish IBS as a more concrete clinical entity, rather than a convenient diagnosis of exclusion applied to explain common GI symptoms.

Emerging Diagnostic Methods

Small Intestinal Bacterial Overgrowth and Breath Testing

New IBS diagnostic techniques are being developed, and their application is helping our understanding of causative factors related to the disorder. Small intestinal bacterial overgrowth (SIBO), a condition in which abnormally high concentrations of enteric bacteria are present in the small intestine, has been reported in as many as 84% of patients meeting diagnostic criteria for IBS.[20,21] The onset of SIBO may be associated with poor clearance of intestinal contents caused by altered intestinal motility.[22] Symptoms associated with SIBO include

carbohydrate malabsorption (eg, lactose intolerance) and excessive production of gas in the small bowel due to bacterial fermentation; these phenomena are consistent with the hallmark IBS symptoms of abdominal pain and bloating. Hydrogen breath testing is a useful method of diagnosing SIBO, and studies have evaluated breath test results in patients with IBS. Fasting patients are administered a small amount of pure carbohydrate (glucose and lactulose are typical substrates, although lactose, fructose, xylose, and sorbitol are administered as well). Bacterial overgrowth results in an increased concentration of hydrogen in exhaled breath, ostensibly due to malabsorption of the carbohydrate and thus, more carbohydrate being available for bacterial metabolism.

A prospective study that evaluated lactulose breath testing as a diagnostic method for SIBO and as a measurement of subsequent response to antibiotic therapy demonstrated that 157 (78%) of 202 patients who met Rome diagnostic criteria for IBS also had SIBO.[20] After they received oral antibiotic therapy (eg, neomycin, ciprofloxacin, metronidazole, doxycycline) for 10 days, 47 patients were given follow-up breath tests and physical examinations. Among 25 patients in whom SIBO had been eradicated (as determined by breath test results), significant improvement in diarrhea and abdominal pain symptoms was achieved ($P < .05$), and 12 patients (48%) in whom SIBO had been eradicated no longer met Rome criteria for IBS ($P < .001$).

A subsequent double-blind, placebo-controlled study demonstrated that 93 (84%) of 111 patients with IBS had abnormal lactulose breath test results at baseline. After 10 days of treatment with either neomycin or placebo, the patients with abnormal breath test results at baseline who received neomycin achieved a 35% improvement in constipation, diarrhea, and abdominal pain symptoms, compared with a 4% improvement achieved by those who received placebo ($P < .01$).[21] Furthermore, normalization of lactulose breath test results in response to neomycin correlated with patient-reported normalization of bowel function. Among patients in whom breath testing indicated eradication of SIBO by neomycin, bowel normalization was improved by 75%, compared with 37% for patients in whom SIBO had not been eradicated by neomycin and 11% for patients who received placebo ($P < .001$).[21] The results of these studies support the administration of lactulose breath tests in IBS diagnosis and the connection between antibiotic eradication of SIBO and relief of IBS symptoms.

Other carbohydrates employed in hydrogen breath testing to identify sugar malabsorption disorders (eg, lactose intolerance) may also have value in diagnosing SIBO associated with IBS. A prospective study showed that 64 (65%) of 98 patients with IBS had abnormal lactulose breath test results and that these 64 patients showed a significant correlation with positive lactose ($P < .05$), fructose ($P < .01$), and sorbitol ($P < .01$) breath test results.[23] A separate study evaluating glucose as a substrate for hydrogen breath testing reported that 20 (31%) of 65 patients with IBS had positive glucose breath test results, compared with 4 (4%) of 102 healthy controls ($P < .00001$).[24] These results suggest that

carbohydrate malabsorption in general (and not with a specific sugar) may be a feature of SIBO that will prove helpful in diagnosing IBS.

Hydrogen breath testing is useful in identifying patients with IBS who are affected with SIBO, but other exhaled gases may have diagnostic benefit as well. A prospective study measured methane concentrations in exhaled air from patients with IBS or IBD (ulcerative colitis or Crohn's disease) who were administered lactulose breath tests.[25] Methane was detected in 50 (17%) of 296 patients with IBS, compared with 2 (3%) of 78 patients with IBD ($P < .01$). In an observational study of 254 patients with IBS who were administered lactulose breath tests, 120 patients (47%) had elevated hydrogen levels, 27 patients (11%) had elevated methane levels, and 14 patients (6%) had elevated levels of both gases.[26] Because methane production is associated with patients with IBS-C, measurement of both methane and hydrogen is important in the diagnosis of IBS.

The diagnostic benefit and noninvasiveness of breath testing in IBS clearly holds promise, but further investigation is required, as not all data support the clinical utility of diagnostic breath testing. A study evaluating hydrogen breath testing in IBS employing lactulose and xylose as substrates demonstrated that only 4 (10%) of 39 patients with IBS had abnormal lactulose test results and 5 (13%) of 39 had abnormal xylose test results.[27] However, the small number of patients in this study and the fact that only hydrogen (not methane) was measured may have affected these results. Breath testing may have an important role as a new diagnostic methodology for IBS, but standardized interpretation of its results remains to be implemented into clinical practice. Lactulose is not absorbed in the GI tract; therefore, lactulose breath test results may reflect the activity of bacteria throughout the entire GI tract and not necessarily overgrowth in the small intestine. Thus, while lactulose breath testing is considered sensitive for SIBO throughout the small bowel, the activity of colonic bacteria may contribute to false positive results. Glucose, however, is normally absorbed by the proximal small intestine, and while glucose breath testing is considered specific for SIBO, overgrowth in the distal small intestine may remain undetected by glucose testing and yield false negative results. The choice of carbohydrates employed in breath testing reflects a potential trade-off between diagnostic sensitivity and specificity.

Given the potential association of SIBO with IBS, breath testing to identify SIBO is a noninvasive and cost-effective alternative to the time-consuming culture and characterization of bacteria from patient stool samples or GI aspirates. However, DNA testing of stool samples may be able to identify and quantify enteric bacterial species contributing to IBS, although this approach is not widely applied in clinical practice. To date, fecal DNA testing studies have demonstrated high variation in bacterial counts from both patients with IBS and control patients,[28,29] but 1 study reported lower concentrations of *Lactobacillus* species in patients with IBS-D than in patients with IBS-C or those in the control group and higher concentrations of *Veillonella* species in patients with IBS-C than those in the control group.[29] Further understanding of bacterial species involved in IBS pathophysiology may lead to fecal DNA testing and bacterial

quantification becoming an important part of patient diagnosis and is likely to improve the diagnostic utility of breath testing as well.

Identifying Other Diagnostic Biomarkers

In addition to developing breath testing as a diagnostic technique, the identification of useful biomarkers for IBS may also improve diagnostic methods by making reliable blood and urine tests possible. While no such tests have been validated in controlled trials or applied in clinical practice, biochemical studies of patients with IBS suggest that blood and urine biomarker testing could potentially be developed to supplement current symptom-based criteria. For example, alterations of the hypothalamic-pituitary–adrenal axis (HPA), an important link between the nervous system and the GI tract, may yield such biomarkers. A study measuring concentrations of HPA peptides reported higher plasma levels of IL-6 and IL-8 ($P < .001$) and cortisol ($P < .05$) in 49 patients with IBS compared with 48 patients in the control group.[30] Measurement of neurotransmitters may also lead to new diagnostic possibilities for IBS. A study demonstrated elevated urinary levels of 5-hydroxyindole acetic acid ($P = .036$) and plasma levels of nitric oxide ($P = .019$) in 19 patients with IBS-D compared with 18 patients in the control group.[31] Understanding the body's physiologic response to IBS may allow blood and urine tests for these or other biomarkers to be developed to help diagnose the disorder, just as further understanding of the underlying causes of IBS, such as the role played by enteric bacteria, is yielding new diagnostic possibilities.

Current Treatment Options for IBS

Further understanding of the pathophysiology of IBS will help identify specific targets for new diagnostic methods and will also contribute to the development of effective treatment options for patients with IBS. Nonpharmacologic treatment options include measures such as diet modification, exercise, and stress reduction. For example, increasing dietary fiber is often recommended to patients with IBS, but the overall efficacy of fiber in relieving GI symptoms is unclear.[32] Pharmacologic therapies administered in the treatment of IBS have traditionally focused on the relief of IBS symptoms,[9,32] but new therapies that target potential underlying causes of IBS are being evaluated.

Pharmacologic Therapies

A variety of drugs are currently administered to relieve symptoms of constipation, diarrhea, and abdominal pain in patients with IBS. Polyethylene glycol increases bowel frequency in patients with IBS who have chronic constipation, but its efficacy in relieving pain and other GI symptoms remains uncertain.[9,33] Antispasmodic agents, such as dicyclomine and hyoscyamine, relax GI muscle tension and may be administered to patients with IBS.[34] Dicyclomine has been shown to help relieve abdominal pain and other IBS symptoms in the short term,[35] but the overall benefit of antispasmodics in the treatment of IBS is unclear.[9] Loperamide, an opioid receptor agonist, is effective

at reducing diarrhea in IBS but does not relieve abdominal pain or distention.[36] Additionally, antidepressants are effective in improving many IBS symptoms,[37] but they may not provide relief of bloating and gas in all patients.

Drugs that affect serotonin receptors are also administered to help improve intestinal motility and relieve symptoms of IBS. The efficacy and safety of alosetron, a serotonin receptor antagonist, and tegaserod, a serotonin receptor agonist, have been evaluated in several clinical trials. In randomized, placebo-controlled clinical trials, alosetron significantly improved abdominal pain in patients with IBS-D or IBS-A compared with placebo,[38-41] with "adequate relief" reported in 41%[39] to 53%[41] of patients who received alosetron ($P \leq .05$ vs placebo). In these trials, alosetron improved diarrhea symptoms, including improved stool frequency and consistency. However, constipation is a frequently reported adverse event with alosetron, occurring in as many as 30% of patients,[39-41] and alosetron is associated with rare but serious GI adverse events including ischemic colitis.[42] Alosetron is only indicated for women with severe IBS-D who have not responded to conventional therapy.[42]

In randomized, placebo-controlled clinical trials, administration of tegaserod 12 mg/d for 4 to 12 weeks provided a modest benefit over placebo in improving IBS symptoms in patients with IBS-C.[43-45] Global relief of IBS symptoms was reported in 44%[44] to 46%[43] of patients who received tegaserod, with significant improvements over placebo reported for constipation symptoms, including bloating and stool frequency and consistency ($P < .05$). Tegaserod, in combination with antibiotics and other agents, is often administered as part of comprehensive therapy to treat IBS symptoms and normalize breath test results.[26,46] However, headache and diarrhea are adverse events associated with tegaserod,[43-45] and additional rare diarrhea-related adverse events have been reported, including hypovolemia, hypotension, and syncope.[47] Furthermore, in early 2007, tegaserod was removed from the market by the US Food and Drug Administration due to a potential increased risk of heart attack, stroke, and chest pain.[48] Because tegaserod is no longer available, other medications that improve intestinal motility, such as erythromycin,[49] may have clinical benefit in managing IBS associated with SIBO.

Overall, alosetron and tegaserod have modest efficacy in relieving diarrhea and constipation symptoms of IBS, respectively, but long-term efficacy and safety of these agents in patients with mild-to-moderate IBS remains questionable.

New Pharmacologic Treatment Options

The efficacy and safety of a number of other agents in IBS therapy are currently under investigation, including fedotozine, trimebutine, lubiprostone, renzapride, asimadoline, and clonidine (Table 2). In a phase 2 study of 238 patients with IBS, the opioid fedotozine 90 mg/d for 6 weeks relieved abdominal pain ($P = .01$ vs placebo),[50] although subsequent studies have not confirmed a clinical benefit.[51] A phase 2 trial (n = 69) reported that trimebutine, an opioid administered for the treatment of migraines, was efficacious in relieving

GI symptoms (P < .0001 vs placebo) by modulating colonic motility in patients with both IBS and gastroesophageal reflux disease, but its overall efficacy in IBS is unclear.[52] Lubiprostone, a chloride channel modulator, is indicated for the relief of chronic constipation,[53] although its efficacy and safety in the treatment of IBS is still being evaluated.[54-56] In a multicenter, phase 3 trial of 1167 patients with IBS-C, 18% of patients who received lubiprostone 16 μg/d for 12 weeks reported "overall response," compared with 10% of patients who received placebo (P = .001).[54] In a separate phase 3 trial, lubiprostone 48 μg/d for 4 weeks significantly improved constipation symptoms (P ≤ .0207) in 46 patients with IBS-C.[55] The serotonin receptor antagonist renzapride is also under investigation for the treatment of IBS-C. A pilot study reported that renzapride 4 mg/d for 28 days significantly reduced GI transit time in 11 patients with IBS-C (P < .05 vs placebo) and provided some relief of abdominal pain and constipation symptoms.[57] However, in another study, renzapride 1 to 4 mg/d for 11 to 14 days significantly reduced colonic transit time in patients with IBS-C (P = .056) but did not significantly improve IBS symptoms.[58] The opioid asimadoline is also being evaluated in the treatment of IBS, although in a study of 20 female patients with IBS, a single 0.5-mg dose of asimadoline did not significantly relieve abdominal pain.[59] Clonidine, an α_2-adrenergic agonist and antihypertensive agent, may have some clinical benefit in patients with IBS-D. An exploratory study (n = 42) demonstrated that clonidine 0.2 mg/d for 4 weeks significantly reduced the severity of diarrhea-related bowel dysfunction compared with placebo (P < .05) but did not significantly improve overall relief of IBS symptoms.[60]

Antibiotics

Given the potential association between SIBO and IBS, and the putative role of enteric bacteria in disease pathology, antibiotics have been investigated in the treatment of IBS. When breath test results were correlated with relief of IBS symptoms, 55 patients who received the systemic antibiotic neomycin 1000 mg/d for 10 days achieved a 35% reduction in severity of IBS symptoms, compared with an 11% reduction in 56 patients who received placebo (P < .05).[21] In the subset of patients with abnormal lactulose breath test results at baseline, 46 patients who received neomycin achieved a 35% reduction from baseline in severity of IBS symptoms, compared with a 4% reduction in 47 patients who received placebo (P < .01). A subsequent study reported that among patients with IBS-C, 19 patients who received neomycin 1000 mg/d for 10 days achieved a mean global improvement in IBS symptoms of 37% from baseline, compared with a 5% improvement for 20 patients who received placebo (P < .001).[61] Additionally, this global improvement with neomycin was most pronounced in the subset of patients who had a positive methane breath test result at baseline. These studies suggest that neomycin may provide relief of IBS symptoms, particularly among patients with constipation-predominant disease.

Successful antibiotic treatment of IBS symptoms in patients with SIBO is correlated with normalization of lactulose breath test results. A retrospective

study of 50 patients with positive breath test results who had been administered the antibiotic rifaximin reported that 31 patients (62%) achieved clinical improvement.[62] Posttreatment breath test results were normal in 81% of these patients who responded to rifaximin, compared with 16% of patients who did not respond to treatment ($P < .001$).

Rifaximin is a nonsystemic antibiotic with broad-spectrum antibacterial activity against enteric pathogens.[63] The minimal bioavailability (<0.4%) of rifaximin restricts its activity to the GI tract and limits the potential occurrence of systemic adverse events and drug-drug interactions.[63-65] Rifaximin has shown efficacy in the treatment of SIBO,[66,67] and its efficacy in the treatment of IBS has been evaluated in several studies. A retrospective chart review of 98 patients with IBS who received antibiotic therapy (median duration of patient time in clinical treatment, 11 months) reported that 58 (69%) of 84 patients who received at least 1 course of rifaximin experienced clinical response, compared with 9 (38%) of 24 patients who received neomycin ($P < .01$) and 27 (44%) of 61 patients who received other antibiotics (eg, augmentin, doxycycline; $P < .01$).[46]

In a randomized, double-blind, placebo-controlled trial, 15 (41%) of 37 patients with IBS who received rifaximin 800 mg/d for 10 days achieved global symptomatic response (ascertained by patient-reported questionnaire), compared with 6 (18%) of 33 patients who received placebo ($P = .04$; Figure 1).[68] After 10 days posttreatment, 10 (27%) of 37 patients in the rifaximin group maintained their symptomatic response, compared with 3 (9%) of 33 patients in the placebo group ($P = .05$). In a second randomized, double-blind, placebo-controlled trial, 43 patients with IBS who received rifaximin 1200 mg/d for 10 days experienced a 36% mean improvement from baseline in the severity of IBS symptoms at 10 weeks posttreatment, compared with a mean improvement of 21% among 44 patients who received placebo ($P = .02$; Figure 2).[69] Additionally, bloating was significantly improved in the rifaximin group compared with the placebo group ($P = .01$). Furthermore, in an open-label, observational study, a 10-day course of rifaximin 1200 mg/d as part of a comprehensive treatment regimen including tegaserod and probiotic therapy improved IBS symptoms in 60% of 81 patients.[26] The positive results of these trials support antibiotic therapy as a clinically useful treatment option in IBS and warrant further investigation into the clinical benefit of nonsystemic antibiotics in patients with IBS.

Probiotics

There is increasing interest in administering probiotics to treat SIBO and IBS.[70] A small, placebo-controlled, 8-week study of probiotic mixture VSL #3 demonstrated no significant benefit over placebo in relieving bloating, pain, bowel frequency, or other GI symptoms in patients with IBS-D (n = 25).[71] However, a randomized, double-blind, placebo-controlled trial of a probiotic mixture containing *Lactobacillus rhamnosus* GG, *L rhamnosus* LC705, *Bifidobacterium breve* Bb99, and *Propionibacterium freudenreichii* ssp. *shermanii* JS reported that 41 patients who received the probiotics achieved a 42% median reduction from baseline in IBS symptom severity, compared with a 6% median reduction in

40 patients who received placebo (P = .015).[72] Additionally, a randomized, double-blind, placebo-controlled trial of the probiotic *Bifidobacterium infantis* 35624 demonstrated that after 4 weeks of treatment, 90 women with IBS who received the probiotics reported significant relief from baseline in abdominal pain, bloating, and bowel dysfunction compared with 92 women who received placebo ($P \leq .05$).[73] These results suggest that probiotic agents, in addition to antibiotics, may normalize bacterial concentrations in the bowel and help relieve symptoms of IBS.

Summary

IBS is a major health problem, and its unknown etiology has traditionally limited diagnostic and treatment techniques to addressing the GI symptoms of the disorder. Symptom-based classifications, including the Manning and Rome criteria, are an important foundation for identifying IBS but are not definitive diagnostic tools. The development of additional diagnostic techniques is an important step toward understanding IBS as a discrete GI disorder, rather than a catch-all diagnosis applied when other conditions have been excluded. Increased understanding of IBS pathophysiology and the identification of factors likely to influence its onset (eg, SIBO) are expanding both diagnostic methodologies and treatment options. In the absence of a reliable biomarker to identify IBS, diagnostic methods such as hydrogen and methane breath testing appear promising but require further investigation to determine their practical utility in the clinical setting. Standardized methodology and interpretation of breath test results is required before breath testing can be included in uniform diagnostic criteria.

Treatment of IBS has traditionally addressed the clinical GI symptoms of the disorder (notably, constipation, diarrhea, and abdominal pain), and while symptomatic relief will remain the principal goal of treatment, new therapies that target the underlying causes of IBS may provide long-term benefit for patients with all types of IBS. Although pharmacologic agents that relieve constipation and diarrhea will continue to benefit patients with IBS, many patients remain unresponsive to traditional therapies. The efficacy and safety of a number of agents are currently being investigated, but the association between SIBO and IBS has suggested that antibiotic and probiotic therapy offer particular promise in disease management. Notably, the nonsystemic antibiotic rifaximin has demonstrated efficacy in improving IBS symptoms, and its favorable safety profile warrants its consideration as a promising addition to the IBS pharmacopeia. Additional study of antibiotics, probiotics, and other agents as treatment options for IBS will no doubt lead to more effective management of this common disorder.

Figure Legends

Figure 1. Proportion of patients with IBS who received rifaximin 800 mg/d (n = 37) or placebo (n = 33) who achieved symptomatic response after 10 days of treatment and at 10 days posttreatment. **P* ≤ .05 vs placebo.[68]

Figure 2. Mean improvement from baseline in symptom severity after 10 weeks posttreatment among patients with IBS who received rifaximin 1200 mg/d (n = 43) or placebo (n = 44) for 10 days. **P* = .02 vs placebo.[69]

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Table 1. Principal Symptom-Based Diagnostic Criteria for IBS

Manning criteria[10]

Abdominal pain relieved by defecation
Looser stools at the onset of abdominal pain
Increased stool frequency with abdominal pain
Abdominal distention
Mucus in stools
Feeling of incomplete evacuation

Rome III criteria[1]

Recurrent abdominal pain or discomfort ≥3 days/month in the last 3 months associated with ≥2 of the following:

Improvement with defecation
Onset associated with change in stool frequency
Onset associated with change in stool form/appearance

IBS, irritable bowel syndrome.

Table 2. Pharmacologic Agents Being Evaluated for the Treatment of IBS

Drug	Therapeutic class	Status
Fedotozine	Opioid	Phase 2
Trimebutine	Opioid	Phase 3
Lubiprostone	Chloride channel modulator	Phase 3 (IBS-C)
Renzapride	Serotonin receptor antagonist	Phase 3 (IBS-C)
Asimadoline	Opioid	Phase 2
Clonidine	α_2-Adrenergic receptor agonist	Phase 2/3 (IBS-D)
Rifaximin	Nonsystemic antibiotic	Phase 2
Dextofisopam	GABA receptor agonist	Phase 2/3
Duloxetine	Serotonin norepinephrine reuptake inhibitor	Phase 4

Linaclotide acetate	Guanylate cyclase-C receptor agonist	Phase 2 (IBS-C)
Solabegron	β_3-Adrenergic receptor agonist	Phase 1

GABA, gamma-aminobutyric acid; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS.