Treatment of Bacterial Overgrowth in Patients With Irritable Bowel Syndrome

Background: Rifaximin is an effective treatment of irritable bowel syndrome (IBS) with small intestinal bacterial overgrowth (SIBO), yet long-term management has not been well studied. Patients with functional bowel symptoms were characterized by lactulose breath test (LBT), and a comprehensive approach to long-term SIBO therapy was employed.
Methods: On day 0, eligible patients completed a baseline symptom questionnaire and were offered rifaximin 1200 mg/d for 10 days followed by tegaserod 3 mg nightly (long-term) plus 1 month of zinc 220 mg/d and a bifidobacteria-based probiotic once daily. Two months later, patients were administered a follow-up questionnaire regarding symptoms at the time of completion of rifaximin therapy and their current symptoms.
Results: 161 of 212 patients with an abnormal LBT met Rome II criteria for IBS. High-methane producers were more likely to have constipation. After completion of rifaximin treatment, ≥50% improvement from baseline was reported by 72% of patients for abdominal pain, 67% for flatulence, 62% for bloating, 58% for constipation, 56% for diarrhea, and 53% for fullness. Similar results were reported at 2 months. Global IBS symptoms at 2 months were reported by 60% of patients to be moderately or greatly improved. Moderately or greatly improved symptoms were more frequent among high-methane producers (83%) than high-hydrogen producers (56%) or high producers of both methane and hydrogen (44%).
Conclusions: Rifaximin treatment followed by adjunctive therapy was associated with sustained improvement in patients with IBS and SIBO. High-methane producers experienced more frequent constipation and reported greater clinical response compared with high-hydrogen producers.

INTRODUCTION

An estimated range of 10% to 85% of individuals with irritable bowel syndrome (IBS) have small intestinal bacterial overgrowth (SIBO) diagnosed by an abnormal lactulose breath test (LBT) result.[1–5] Disruption of the normal small bowel bacterial population secondary to dysmotility in IBS may result in gas, bloating, flatulence, and altered bowel function.[6] Antibiotic eradication of SIBO, with recent studies correlating normalization of the LBT result, has resulted in symptomatic improvement in IBS.[1–3,7–15] Persistence of an underlying motility disorder of the migrating motor complex in IBS is thought to be responsible for SIBO and symptom relapse.[6,16] Intestinal permeability has been demonstrated to be a persistent problem in postinfectious IBS and may have a role in the inflammatory and hypersensitivity components of IBS.[6,17–18]

Treatment of bacterial overgrowth and IBS with a nonabsorbable antibiotic followed by subsequent prokinetic and intestinal permeability therapy has not been evaluated. The objective of the current study was to assess functional bowel symptoms and characterize patients according to LBT results. This study assessed the response to medical therapy directed at acute treatment and the prevention of recurrence of SIBO.

METHODS

Patients

Patients visiting a private, suburban gastroenterology clinic from June to October 2005 were eligible for treatment with study medication if they had functional bowel symptoms that met all Rome II criteria for IBS diagnosis[19] and if they had an abnormal LBT result, as defined by Pimentel et al.[3] Patients were excluded if they had active organic gastrointestinal disease (eg, celiac disease, pancreatic insufficiency, Crohn's disease, and ulcerative colitis) on the basis of

medical history, physical exams, testing with tissular transglutaminase and total immunoglobulin A for celiac disease, and colonoscopy at study entry.

Study Design and Procedures

This prospective, observational study was conducted at a private gastroenterology group practice. After an overnight fast, patients with functional bowel symptoms of abdominal pain, diarrhea, constipation, bloating, or flatulence visited the clinic on day 0 for symptom assessment and administration of the LBT. As part of the symptom assessment, patients were asked to indicate if they had experienced any abdominal pain, diarrhea, constipation, abdominal bloating, fullness after meals, flatulence, or belching during the previous 7 days. After patients completed the symptom assessment on day 0, the LBT was administered. After a baseline end-expiratory breath sample was obtained, patients drank 10 g lactulose powder (Kristalose™; Mylan Bertak Pharmaceuticals, Inc, Research Triangle Park, NC) in 240 mL water. Breath samples were collected at 15-minute intervals for the ensuing 180 minutes. Samples were analyzed for hydrogen and methane by gas chromatography (QuinTron DP Plus; QuinTron Manufacturing, Milwaukee, Wis).

On day 0, eligible patients completed a baseline symptom questionnaire and were offered rifaximin (Xifaxan®; Salix Pharmaceuticals, Inc, Morrisville, NC) 1200 mg/d for 10 days followed by tegaserod (Zelnorm®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) 3 mg nightly (prescribed for long-term use) plus 1 month each zinc 220 mg/d and a bifidobacteria-based probiotic (Flora-Q®; Kenwood Therapeutics, Fairfield, NJ) once daily. Approximately 2 months after day 0, patients were administered a follow-up questionnaire on which they were asked to indicate, for each functional gastrointestinal symptom present at baseline (ie, abdominal pain, diarrhea, constipation, abdominal bloating, fullness after meals, flatulence, and belching), the percentage of improvement immediately after finishing rifaximin treatment (ie, 10 days after day 0) and at the present time (ie, at the time the questionnaire was completed, approximately 2 months after day 0). In addition, patients were asked to rate their overall symptom improvement at the present time as greatly improved, moderately improved, mildly improved, or no improvement.

Endpoints and Data Analysis

The primary prospectively defined endpoint was the percentage of patients with moderately or greatly improved overall symptoms at 2 months after initiation of the treatment regimen. Other prospectively defined endpoints were (1) the percentage of patients with ≥50% improvement in the individual symptoms of abdominal pain, diarrhea, constipation, abdominal bloating, fullness after meals, flatulence, and belching among patients who had these symptoms at baseline; and (2) the mean percent improvement in individual symptoms of abdominal pain, constipation, bloating, flatulence, and diarrhea among patients with the symptom at baseline. These frequencies were calculated for symptoms at both 10 days and 2 months after initiation of the treatment regimen. Descriptive statistics were used to summarize data for patients with both baseline and follow-up data. Demographics, presence of baseline symptoms, and results for the study endpoints, with the exception of mean percent improvement, were summarized as a function of IBS diagnosis and as a function of breath test result (hydrogen-positive, methane-positive, methane/hydrogen-positive). Mean percent improvement was summarized as a function of breath test result only.

RESULTS

Patients and Breath Test Evaluations

Of 339 patients with functional bowel symptoms screened, 212 (63%) had an abnormal LBT result. In 11 (3%) of the 339 patients, the LBT produced a flatline response (ie, <5 ppm increase in hydrogen or methane over 180 minutes), an abnormal result reflecting hydrogen sulfide production. These patients were excluded from further evaluation. Among patients with an abnormal breath test result at baseline, an abnormal result was observed at 90 minutes in 75% of patients. The remaining 25% of patients required further breath analysis over the 180-minute period before an abnormal result was obtained. The majority of patients with an abnormal LBT result had a high-hydrogen result (75%). Of the 212 patients with an abnormal LBT result, 161 (76%) met Rome II criteria for IBS. Of these 161 patients, 82 (51%) returned evaluable follow-up data and were included in data summaries (Table 1). The mean time between initiation of treatment and completion of the follow-up questionnaire was 64.5 (± 41.8) days.

Baseline Symptoms

The most common symptoms at baseline among 82 patients who provided baseline and follow-up data were abdominal pain, bloating, and flatulence (Table 2). At baseline, 79% of patients complained of constipation, and 72% complained of diarrhea. Additionally, high-methane producers were more likely to have constipation (83%) than diarrhea (50%), whereas diarrhea and constipation were similarly common among high-hydrogen producers.

≥50% Improvement in Functional Bowel Symptoms

After completion of rifaximin treatment (10 days after day 0), ≥50% improvement from baseline was reported by 72% of patients for abdominal pain, 62% for bloating, 67% for flatulence, 56% for diarrhea, 58% for constipation, and 53% for postprandial fullness (Figure 1). A similar pattern of results was reported for symptoms experienced at 2 months after beginning treatment regimen (Figure 1). For symptoms 10 days or 2 months after initiation of the treatment regimen, high-methane producers were more likely to report ≥50% improvement with adjunctive rifaximin therapy than high-hydrogen producers for all symptoms except diarrhea and belching (Figure 2).

Frequency of Moderately or Greatly Improved Symptoms

The percentage of patients reporting moderately or greatly improved overall symptoms at 2 months with adjunctive rifaximin therapy was 60% (Figure 3). Moderately or greatly improved overall symptoms were more frequent among high-methane producers (83%) than among high-hydrogen producers (56%) or high producers of both methane and hydrogen (44%) (Figure 3).

Mean Percent Improvement in Individual Symptoms

Among patients who responded to the questionnaire and had the relevant symptom at baseline (n = 82), mean percent improvement in symptoms at 10 days was 62% for abdominal pain, 53% for constipation, 52% for bloating, 53% for flatulence, and 62% for diarrhea. The corresponding percent improvements in symptoms at 2 months were 58% for abdominal pain, 50% for constipation, 52% for bloating, 51% for flatulence, and 55% for diarrhea. For each symptom, greater mean percent improvement was reported among high-methane producers (67%–84% at 10 days and 61%–82% at 2 months) than among high-hydrogen producers (46%–58% at 10 days and 43%–53% at 2 months).

DISCUSSION

The results of this observational study are consistent with a growing evidence base suggesting that SIBO contributes to IBS symptoms that are amenable to treatment with SIBO-eradicating antibiotics. In the current study and in previous studies,[1–3,7,20] the frequency of SIBO was high among patients presenting with functional bowel symptoms. Among 254 patients meeting Rome II criteria for IBS, 63% had an abnormal LBT result, reflecting the presence of SIBO. A similar percentage of patients with functional bowel symptoms not meeting Rome II criteria had an abnormal LBT result.[15]

This study corroborates previous findings that the LBT gas profile can predict symptom presentation,[21,22] although this observation should be interpreted cautiously given the small number of patients in high-methane subgroups in the current study. In individuals with IBS and SIBO, high-methane producers were more likely to have constipation than diarrhea. Methane has been shown to slow intestinal transit and to reduce postprandial plasma concentrations of serotonin, which mediates peristalsis.[23,24]

In this study, high-methane producers responded better to SIBO therapy than high-hydrogen producers. Moderately or greatly improved overall symptoms 2 months after initiation of comprehensive SIBO therapy were reported by 83% of high-methane producers compared with 56% of high-hydrogen producers and 44% of high producers of both methane and hydrogen. In addition, for individual symptoms, greater mean percent improvement was reported among high-methane producers than among high-hydrogen producers. Together, the results suggest that the LBT profile is clinically important both in predicting clinical symptoms (constipation-predominant vs diarrhea-predominant) and in predicting response to therapy. These possibilities warrant further investigation with a larger number of patients.

Treatment with rifaximin followed by adjunctive SIBO therapy was associated with substantial improvement of functional bowel symptoms in patients with a diagnosis of both IBS and SIBO. The percentage of patients reporting moderate or great improvement in symptoms approximately 2 months after initiation of the treatment regimen was 60%, a substantial response despite not having a comparative placebo arm. The degree to which rifaximin treatment alone accounted for the prolonged improvement in functional bowel symptoms observed in this study cannot be determined given the observational design and the subsequent administration of probiotic, zinc, and tegaserod. Nonetheless, eradication of SIBO by rifaximin and improvement of functional bowel symptoms, as demonstrated in both controlled and open-label IBS studies,[1,2,9,10] is consistent with the possibility that rifaximin contributed to symptom improvement in the current study.

The second phase of SIBO therapy in this study appears to have maintained symptomatic improvement. Long-term tegaserod was given in an attempt to improve the phase III abnormality of the migrating motor complex found in patients with IBS who have SIBO.[17] Zinc was prescribed for 1 month to help reverse defects in small intestinal permeability.[17,24] The bifidobacteria-based probiotic was prescribed to help repair the reported small intestinal permeability and immune defects characteristic of SIBO, IBS, and postinfectious IBS.[17,18,25]

The results of this study should be interpreted cautiously given the aforementioned observational design, which limits the ability to attribute improvements to the treatment regimen. In addition, because the follow-up questionnaire used to assess symptoms at the time of completion of rifaximin (ie, 10 days after day 0) took place approximately 2 months after day 0, recall bias might have affected patients' ratings of early symptom improvement. Patient compliance may also have impacted the results of the study (questionnaires were returned by 82 of the 161 treated IBS patients who had an abnormal LBT result). Furthermore, the extended intervals required to obtain breath test results could have impacted the study findings. An estimated 25% of patients required the entire 180 minutes of breath analysis to achieve an abnormal result.

In this study, treatment of functional bowel symptoms with rifaximin and adjunctive SIBO therapy was associated with symptomatic improvement among patients with an abnormal LBT result and a Rome II diagnosis of IBS. These results support findings of a double-blind, placebo-controlled trial in which rifaximin 1200 mg/d for 10 days substantially improved global symptoms of IBS compared with placebo (37% vs 20%, respectively).[10] The current study is the first to evaluate comprehensive SIBO therapy in IBS directed at all defects attributed to SIBO pathophysiology (eg, bacterial excess, decreased motility, increased permeability, altered immunity). Benefits were sustained over a mean follow-up period of at least 2 months, and improvement was generally more marked among high-methane producers than high-hydrogen producers. This study supports further investigation of the potential benefits of SIBO therapy in functional bowel disorders.

Table 1. Patient Characteristics and Breath Test Results (n = 161)

Female, n (%)	134 (83)
Mean age (range), y	50 (10–85)[a]
Breath test result, n (%)	
High hydrogen	120 (75)
High methane	27 (17)
High hydrogen and methane	14 (9)

[a] *160 patients ≥ 18 y of age; 1 patient 10 y of age.*

Table 2. Baseline Symptoms in Patients with IBS and Abnormal LBT

Symptom	Patients, n (%)			
	Total (n = 82)	High Hydrogen (n = 55)	High Methane (n = 18)	High Hydrogen and Methane (n = 9)
Abdominal pain	82 (100)	55 (100)	18 (100)	9 (100)
Diarrhea	59 (72)	44 (80)	9 (50)	6 (67)
Constipation	65 (79)	44 (80)	15 (83)	6 (67)
Bloating	77 (94)	51 (93)	17 (94)	9 (100)
Fullness	66 (80)	43 (78)	15 (83)	8 (89)

Flatulence	72 (88)	47 (85)	16 (89)	9 (100)
Belching	46 (56)	31 (56)	8 (44)	7 (78)

IBS = irritable bowel syndrome; LBT = lactulose breath test.

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FIGURE LEGENDS

Figure 1. Majority of patients reported ≥50% improvement in all symptoms from baseline, except belching at 10 days, and belching and diarrhea 2 months after initiation of rifaximin treatment.
Figure 2. High-methane producers reported ≥50% improvement in baseline symptoms more frequently than high-hydrogen producers 10 days after initiation of rifaximin treatment for all symptoms except diarrhea and belching.
Figure 3. Percentage of patients reporting moderately or greatly improved symptoms 2 months after initiation of rifaximin treatment. Data are for patients with symptoms at baseline.

Irritable Bowel Syndrome: Emergence of New Diagnostic and Treatment Options

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. *Aim:* 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. *Results:* 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, which must be examined further before their clinical relevance and impact on treatment algorithms is clear. Further understanding of the body's physiologic response to IBS may identify diagnostically relevant biologic markers. Current treatment options for IBS are administered to relieve constipation and diarrhea, but many patients remain unresponsive to these therapies. Nontraditional therapies, such as antibiotics (eg, rifaximin), may target SIBO as an underlying cause of IBS and have shown efficacy in

disease management. Given these positive results, IBS treatment options will likely expand beyond mere management of clinical symptoms. *Conclusions:* 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.

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), diarrhea-predominant (IBS-D), or involve alternating or mixed periods of both (IBS-A or IBS-M).[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 IBS sufferers 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, 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 new options for clinicians while helping to elucidate the pathophysiology of this common disorder. As IBS 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 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, 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 abnormalities,[14,15] are not included in the diagnosis algorithm.

Supplemental diagnostic tests may be performed by clinicians to confirm and diagnose IBS, often by excluding disorders with similar symptomologies. Blood tests may be performed to detect anemia and other abnormalities consistent 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 testing 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 evaluating lactulose breath testing as a diagnostic method for SIBO, and as a measurement of subsequent response to antibiotic therapy,

demonstrated that 157 of 202 patients (78%) meeting Rome diagnostic criteria for IBS also had SIBO.[20] After receiving 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), 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 of 111 patients (84%) 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] 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 of 98 patients (65%) 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 of 65 patients (31%) with IBS had positive glucose breath test results, compared with 4 of 102 healthy controls (4%, $P < .00001$).[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 IBS patients 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 inflammatory bowel disease (IBD; ulcerative colitis or Crohn's disease) who were administered lactulose breath tests.[25] Methane was detected in 50 of 296 patients (17%) with IBS, compared with 2 of 78 patients (3%) 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] Therefore, while methane breath testing may be an effective new tool for diagnosing GI abnormalities, it appears that hydrogen breath testing is a more sensitive assay for IBS. However, methane production may be associated with patients with IBS-C, and therefore, measurement of both gases 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 of 39 patients (10%) with IBS had abnormal lactulose test results, and 5 of 39 (13%) 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, and therefore lactulose breath test results may reflect the activity of bacteria throughout the entire GI tract, and not necessarily overgrowth of 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 of 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 IBS and control patients,[28,29] but one study reported lower concentrations of *Lactobacillus* species in IBS-D patients than in IBS-C patients or controls, and higher concentrations of *Veillonella* species in IBS-C patients than controls.[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 IBS patients compared with 48 controls.[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 IBS-D patients compared with 18 controls.[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 IBS patients, 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 IBS patients. Polyethylene glycol increases bowel frequency in IBS patients with 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]

Drugs that affect serotonin receptors are also administered to help 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,[37–40] with "adequate relief" reported in 41%[38] to 53%[40] 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 reported with alosetron, occurring in as many as 30% of patients,[38–40] and alosetron is associated with rare but serious GI adverse events including ischemic colitis.[41] Alosetron is only indicated for women with severe IBS-D who have not responded to conventional therapy.[41]

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.[42–44] Global relief of IBS symptoms was reported in 44%[43] to 46%[42] of patients who received tegaserod, with significant improvements over placebo reported for constipation symptoms including bloating and stool frequency and consistency ($P < .05$). However, headache and diarrhea are adverse events associated with tegaserod,[42–44] and additional rare diarrhea-related adverse events have been reported, including hypovolemia, hypotension, and syncope.[45] 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 unclear.

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),[46] although subsequent studies have not confirmed a clinical benefit.[47] 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.[48] Lubiprostone, a chloride channel modulator, is indicated for the relief of chronic constipation,[49] although its efficacy and safety in the treatment of IBS is still being evaluated.[50,51] In a phase 3 trial, lubiprostone 48 μg/d for 4 weeks significantly improved constipation symptoms (P ≤ .0207) in 46 patients with IBS-C.[50] 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.[52] 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.[53] 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.[54] 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.[55]

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 receiving 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 receiving placebo (P < .05).[21] In the subset of patients with abnormal lactulose breath tests 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 administered 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 administered placebo (P < .001).[56] Additionally, this global improvement with neomycin was most pronounced in the subset of patients who had a positive methane breath test at baseline. These studies suggest that neomycin may provide relief of IBS symptoms, particularly among patients with constipation-predominant disease.

Rifaximin is a nonsystemic antibiotic with broad-spectrum antibacterial activity against enteric pathogens.[57] 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.[57–59] Rifaximin has shown efficacy in the treatment of SIBO,[60,61] and its efficacy in the treatment of IBS has been evaluated in several studies.

A retrospective chart review of 98 patients with IBS receiving antibiotic therapy (median duration of patient time in clinical treatment, 11 months) reported that 58 of 84 patients (69%) who received at least 1 course of rifaximin experienced clinical response, compared with 9 of 24 patients (38%) who received neomycin ($P < .01$) and 27 of 61 patients (44%) who received other antibiotics (eg, augmentin, doxycycline; $P < .01$).[62]

In 1 randomized, double-blind, placebo-controlled trial, 15 of 37 patients (41%) with IBS who received rifaximin 800 mg/d for 10 days achieved global symptomatic response (ascertained by patient-reported questionnaire), compared with 6 of 33 patients (18%) who received placebo ($P = .04$; Figure 1).[63] After 10 days posttreatment, 10 of 37 patients (27%) in the rifaximin group maintained their symptomatic response, compared with 3 of 33 patients (9%) 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).[64] Additionally, bloating was significantly improved in the rifaximin group compared with placebo ($P = .01$). Additionally, 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.

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 criteria, including the Manning and Rome algorithms, are an important foundation for reliably diagnosing IBS, but 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 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 all types of IBS patients. 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 therapy offers

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 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 administered rifaximin 800 mg/d (n = 37) or placebo (n = 33) who achieved symptomatic response after 10 days of treatment and at 10 days posttreatment. *$P \leq .05$ vs placebo.[63]

Figure 2. Mean improvement 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.[64]

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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 2
Lubiprostone	Chloride channel modulator	Phase 3 (IBS-C)
Renzapride	Serotonin receptor antagonist	Phase 3 (IBS-C)
Asimadoline	Opioid	Phase 3
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.

INFORMATION FOR INTRODUCTION / DISCUSSION

Restless legs syndrome (RLS) is characterized by an urge for leg movement, often with abnormal leg sensations. Symptoms are triggered by rest, often at night, and improve temporarily with movement, especially walking. The prevalence ranges from 7% to 15% and significantly contributes to sleep disorders (Allen 2005, Berger 2004; Lavigne 1994). The prevalence increases with age, increased body mass index, lower income, and smoking (Phillips 2000). RLS may be a primary disorder (including familial, genetic, and neuropathy-associated forms) or

associated with a variety of diseases and conditions which are often associated with iron deficiency (Montplaisir 1985, Trenkwalder 1996, Ondo 1996; Iannaccone 2000, Hening 2004, Rama 2004, Liebetanz 2006).

Cerebral iron deficiency has been implied as a common contributing factor to all forms of RLS (Earley 2000, Allen 2001, Earely 2006). Increasing evidence points to fundamental abnormalities of iron processing in RLS (Wang 2003), and since the D2 receptor requires iron as a cofactor, and pharmacological agents acting upon the D2 receptor are among the most effective treatments for RLS symptoms (Walters 2004). CSF ferritin has been demonstrated to be lower and transferrin higher in RLS patients than control patients (Earely 1999), and regional brain iron concentration assessed through MRI demonstrated a significant decrease in brain iron concentrations in the substantia nigra and to a lesser extent the putamen of RLS patients (Allen 2001, Earely 2006). Neuropathological examination of autopsy brains of seven patients with RLS found a decrease in iron staining in the substantia nigra and decreased staining for H-ferritin, divalent metal transporter 1, transferrin receptor, and transferrin (Connor 2003). Ferroportin, the main cellular iron export mechanism for enterocytes and macrophages, exhibited minimal staining in RLS patients. Iron regulatory protein 1, which stabilizes TfR mRNA in settings of low iron, was reduced by 45% in RLS patients (Connor 2004). CSF ferritin level reduction argues for loss of iron storage capacity in the brain in RLS (Clardy 2006).

Most RLS patients do not have a complete peripheral laboratory panel characteristic for iron deficiency or have anemia (Aul 1998, Sun 1998, Berger 2002). In 365 RLS patients no associations with ferritin or soluble transferring receptor were seen (Berger 2002). In 113 RLS patients, 77.1% had low iron saturation, 62.5% had low serum iron, 25% had low serum ferritin and 21.2% were anemic (Aul 1998). In 27 RLS patients, 17 patients had ferritin under 50 but

only 3 were under 10 and only 4 patients had low iron saturation (Sun 1998). In the last study, the severity of RLS was associated with a ferritin level lower than 50. Administration of iron produces improvement (O'Keeffe 1994) but may be incomplete and transient (Earley 2005; Sloand 2004).

The cause of iron abnormalities in RLS remains to be elucidated. While the primary source of the dysregulation of iron metabolism in RLS remains unknown, a recently discovered candidate is hepcidin. Hepcidin is a cysteine-rich peptide that has antimicrobial properties that derived its name because of its origin in the liver (Ganz 2006). It is believed to be the principal iron stores regulatory hormone and regulates dietary iron absorption by the duodenal crypt cells and reticuloendothelial macrophages (Frazer 2005). Induction of hepatic hepcidin mRNA with iron overload results in suppression of duodenal cytochrome B (DcytB) and DMT1 with resultant reduction in iron absorption (Frazer 2002). In addition, ferroportin in macrophages is down-regulated by hepcidin (Delaby 2005). A variety of experiments have established the role of hepcidin, as a key mediator of hypoferremia in inflammation (Nicholas 2002). Infection and inflammation both induce hepcidin expression. The increase in hepcidin in response to inflammatory stimuli is rapid, with lipopolysaccharide injections inducing peaks in urinary hepcidin within 6 hours, followed by a 57% drop in serum iron after 22 hours (Kemna 2005).

One theory that would tie diseases associated with SIBO to RLS is that translocation of lipopolysaccharides could alter hepcidin resulting in abnormal central processing of iron. Another theory is that the inflammatory cytokines released by SIBO directly irritate the muscles. Finally, muscle intracellular iron levels could be affected and this could result in symptoms of RLS. Iron deficiency can affect cell oxygenation by indirect mechanisms (e.g., functioning of mitochondrial iron-containing proteins required to process oxygen in cells)

(Alpers 2003). We theorize that the latter may be one mechanism to explain RLS muscle discomfort that is relieved by leg movement which could improve blood circulation.

In a pilot study of patients with irritable bowel syndrome (IBS) and indirect evidence of small intestinal bacterial overgrowth (SIBO) we found that rifaximin, a non-absorbable, small-intestine targeting, broad spectrum antibiotic (Huang 2005, Lauritano 2005) was effective in improving RLS and gastrointestinal symptoms (Weinstock 2007). Ten of 13 patients studied exhibited ≥80% RLS improvement and all who had significant relief stated the effect started during or at the end of rifaximin. The treatment concept was based on emerging data that IBS and associated conditions such as fibromyalgia are caused by SIBO (Lin 2004) and that if RLS was associated with fibromyalgia, then IBS with SIBO could be associated with RLS.

The following medical conditions associated with an increased prevalence of RLS also have an increased incidence of SIBO: gastric surgery (Banerji 1970, Eckbom 1960, Browning 1974), older age (Phillips 2000, McEvoy 1983, Arranz 1992, Haboubi 1992, Husebye 1992, Hutchinson 1997), fibromyalgia (Yunus 1996, Pimentel 2004), diabetes (Gemignani 2007, Virally-Monod 1998), end stage renal disease (Gigli 2004, Siddiqui 2005, Strid 2003), rheumatoid arthritis (Salih 1994, Auger 2005, Henriksson 1993, scleroderma (Prado 2002, Soudah 1991), Parkinson's disease (Nomura 2006, Lupasci 2005), hypothyroidism (Collado-Seidel 1999, Laurentin 2005) and chronic liver disease (Ashwathnarayan 2006, Yang 1998, Chang 1998, Pardo 2000).

Evidence is accumulating that suggests that SIBO is associated with systemic inflammation and may be an alternative explanation for the development and persistence of IBS, fibromyalgia, and other hypersensitivity syndromes (Chadwick 2002, Pimentel 2004, Lin 2004, van der Veek 2005, Riordan 1996, Barbara 2004). SIBO may be a subtle condition as opposed to

the typical gastrointestinal symptoms seen in the bacterial overgrowth syndrome (Henriksson 1993). Increased levels of inflammatory cytokines associated with SIBO (and with IBS) do not necessarily require gross evidence of a malabsorption disease (Chadwick 2002, Dunlap 2006).

In this report we test the hypotheses that a chronic inflammatory state associated with SIBO causes increased intraleukin-6 levels which result in elevated hepcidin levels (Raja 2005, Ganz 2006). On its own account, IL-6 has been shown to be an important regulator of sleep (Vgontzas 2002, Vgontzas 2005). Hepcidin is the regulatory peptide produced by the liver and has been previously studied as a factor in explaining abnormal iron processing in RLS (Connor 2003, Connor 2004, Clardy 2006).