Clinical Roundtable Monograph

An Evidence-based Approach to Therapy in IBS-D: A Case Study Compendium

Faculty

Lin Chang, MD
David Geffen School of Medicine at UCLA
Los Angeles, California

Brian E. Lacy, PhD, MD
Section of Gastroenterology and Hepatology
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire

Brennan M. R. Spiegel, MD, MSHS
VA Greater Los Angeles Healthcare System
David Geffen School of Medicine at UCLA
Los Angeles, California

Abstract

A burden on both patients and the healthcare system, irritable bowel syndrome (IBS) is a prevalent condition that can result in high medical costs, frequent visits to the doctor, missed work, and anxiety and depression in the patient. This chronic disorder causes abdominal pain or discomfort and is characterized by abnormal defecation that presents mainly as either constipation or diarrhea symptoms. IBS associated with diarrhea (IBS-D) accounts for approximately one third of all IBS patients. IBS-D treatment can be confusing and frustrating for both the patient and the physician, complicated by the fact that a specific therapeutic algorithm has not been developed. Treatment options are widely varied, consisting of both nonpharmacologic (dietary changes) and pharmacologic (loperamide and alosetron) interventions. Furthermore, mounting evidence suggests a possible role for small intestinal bacterial overgrowth in the pathogenesis of IBS-D; thus, both antibiotics (such as rifaximin) and probiotics are frequently used to treat patients. Although all of these interventions elicit some measure of symptom response in a proportion of treated patients, there is no standard of care for the treatment of IBS-D. Thus, physicians would benefit from knowledge of all of the strategies used to treat IBS-D, in order to treat patients appropriately.

Introduction

Brian E. Lacy, PhD, MD

Irritable bowel syndrome (IBS) is a highly prevalent disorder that reduces patients' quality of life and imposes a significant economic burden to the healthcare system. The prevalence of IBS in the United States is estimated to be 9–22%,[1-3] and the yearly incidence is approximately 1.5%.[4] IBS is one of the most common medical disorders encountered by all healthcare providers, with 12–14% of all primary care patient visits and up to 33% of all referrals to gastroenterologists involving the evaluation and treatment of IBS.[5,6]

IBS has a significant economic impact on both patients and society, with annual costs (both direct and indirect) estimated at $15–30 billion dollars in the United States alone.[7-9] This extraordinary expense is primarily due to absenteeism from school and work, more frequent healthcare visits, the presence of comorbid conditions (including overlapping dyspepsia, reflux, migraine headaches, and fibromyalgia), extensive medication use, and unnecessary surgery. It is estimated that annual medical costs are 49–51% higher for IBS patients than for non-IBS patients.[10-12]

A number of studies have shown that patients with IBS have a reduced quality of life. Using the SF-36 validated short form health survey, Gralnek and colleagues found that IBS patients (n=877) had a significant reduction in quality of life compared to the general population ($P<.001$), as well as compared to patients with gastroesophageal reflux, diabetes, and dialysis-dependent end-stage renal disease.[13] Similar findings were noted in a study of 257 patients with severe IBS,[14] whereas another report found that IBS patients had reduced quality-of-life scores compared to patients with gastroesophageal reflux disease, asthma, and migraine headaches ($P<.003$).[15]

The Rome III Committee defines IBS as a chronic disorder characterized by abdominal pain or discomfort associated with disordered defecation (either constipation [IBS-C], diarrhea [IBS-D], or mixed/alternating symptoms of constipation and diarrhea [IBS-M]).[16] To meet the criteria, symptom onset should be at least 6 months before the patient is first seen for formal evaluation. Abdominal pain or discomfort should be present at least 3 days per month for 3 months and should be associated with 2 or more of the

Table 1. Rome III Criteria for the Diagnosis of Irritable Bowel Syndrome

- **Symptom onset at least 6 months prior to diagnosis**
- **Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following:**
  - Improvement with defecation
  - Onset associated with a change in stool frequency
  - Onset associated with a change in stool form (appearance)
- **One or more of the following symptoms on at least one quarter of occasions for subgroup identification:**
  - Abnormal stool frequency (<3/week)
  - Abnormal stool form (lumpy/hard)
  - Abnormal stool passage (straining, incomplete evacuation)
  - Bloating or a feeling of abdominal distension
  - Passage of mucous
  - Frequent, loose stools

Modified from Longstreth GF, et al.[16]

following factors: improvement with defecation; onset associated with a change in stool frequency; and onset associated with a change in stool form (Table 1).

Many healthcare providers find that treating patients with IBS-D, which accounts for approximately one third of all IBS patients, can be particularly challenging and frustrating. This treatment challenge arises mainly because a specific algorithm for the treatment of IBS-D does not exist, treatments are not uniformly effective in all patients, recommendations continually change, and new therapeutic options have recently become available. This roundtable was convened so that a panel of experts could review current treatment options for patients with IBS-D. Each of the expert panel members presented a patient case to illustrate a particular issue in patient management, followed by a brief discussion; the panel members then participated in a question-and-answer session.

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Diet and Probiotics in the Management of IBS-D Patients

Brian E. Lacy, PhD, MD

A 27-year-old single man with no children was referred for a second gastroenterology consult for the treatment of presumed IBS-D. The patient had no gastrointestinal symptoms until 1 year ago when he went on a cruise vacation with friends. During the vacation, all the individuals developed nausea, vomiting, and diarrhea; however, his friends all recovered completely while he did not. Instead, the patient had persistent gastrointestinal symptoms, including bloating, cramping, and frequent loose and watery nonbloody stools. Upon seeing an internist, stool studies and laboratory tests were obtained and deemed completely normal. The patient then went to his gastroenterologist, who performed a colonoscopy with random biopsies throughout the colon; findings from this procedure were also completely normal. Because the patient was experiencing pain, a computed tomography (CT) scan was used to visualize the abdomen and pelvis; again, these findings were normal. A follow-up appointment with his gastroenterologist involved repeated blood work, including serologic tests for celiac disease. There were no significant findings.

Upon referral for a second gastroenterology consult, the patient's physical examination was completely normal, aside from some mild tenderness in the area over the sigmoid colon. The patient reported that his mother had IBS-D but said that no first-degree family members had celiac disease

or inflammatory bowel disease (IBD). The patient's weight had remained stable, and he had no other medical or surgical issues.

Prompted by his own research, the patient decided to alter his diet to include more fruits, vegetables, and whole grains. However, these diet modifications did not appear to help his condition; in fact, some of his symptoms worsened. Thinking that his symptoms could be explained by celiac disease (despite his previously negative test), he stopped eating wheat-containing foods for 1 month. Again, he had no symptom improvement. The patient told his second gastroenterologist that he would prefer to avoid prescription medication for symptom resolution. He was receptive to alternative or natural medications, as well as dietary alterations.

Dietary Modifications

It is a common belief among IBS patients that diet plays a significant role in their symptoms.[1] Thus, they conclude that avoiding specific foods may reduce their symptoms. For example, a survey of 84 patients with IBS found that nearly two thirds (62%) limited or excluded food items (an average of 2.5) from their diet.[2] In a separate survey of 1,242 IBS patients, 52% thought that IBS was caused by a lack of digestive enzymes and 63.3% were interested in learning about foods to avoid.[3]

The role of diet in IBS-D symptoms is disputed, with opinions differing on the basis of anecdotal evidence and clinical investigation.[4] Clinical trials investigating dietary changes are complicated due to inadequate controls. Several lines of evidence support an overall dietary impact on IBS symptoms. For example, over half (63%) of IBS patients report that their symptoms worsen following a meal.[5] A 10-day fast (except for water) produced a significant improvement in several IBS symptoms, including abdominal pain/discomfort, abdominal distension, diarrhea, anorexia, and nausea, among IBS inpatients with moderate-to-severe symptoms.[6] According to a recent review of the subject by Heizer and colleagues, published reports suggest that IBS symptoms may be caused or worsened by 1 or more dietary components in approximately 25% of patients.[4] Several foods and/or dietary components have been implicated in IBS symptoms. Some of these have been investigated for the potential to improve symptoms, whereas others are thought to worsen symptoms. However, it is important to note that, if complete symptom resolution occurs after a patient avoids a particular food or dietary component, it is probable that the patient suffers from a dietary intolerance rather than IBS.

Traditionally, insufficient dietary fiber has been long held as a primary cause of IBS.[7] Despite the fact that numerous anecdotal reports have stated that cereal fiber worsened symptoms, fiber remains one of the most extensively studied dietary components in IBS. Systematic reviews and comprehensive meta-analyses of the available evidence have concluded that, while published studies suffer from heterogeneous populations and a strong placebo effect, it is evident that fiber is largely not efficacious for the treatment of IBS.[4] Any limited benefit is restricted primarily to patients who have IBS-C.[8-10] In contrast, patients with IBS-D actually tend to experience symptom improvement when they decrease the amount of fiber in their diet. Additionally, the type of dietary fiber appears to be important in its ability to elicit an effect, with soluble fiber providing a greater benefit than insoluble fiber.[11]

A number of carbohydrates have been investigated for their role in the development of IBS symptoms. Lactose, a disaccharide, is the most common poorly digested and malabsorbed of these carbohydrates worldwide. The true prevalence of lactose intolerance is unknown and complicated by differing definitions of intolerance versus malabsorption, as well as varying incidences in racial and ethnic populations. The lowest frequency of lactose intolerance occurs in whites from northern Europe, North America, and Australia (~5%), whereas very high rates (75–90%) have been reported in black, Native American, and Asian populations.[12] Symptoms of lactose intolerance include bloating, flatulence, abdominal discomfort, nausea, and loose stools. Several studies have investigated the importance of lactose malabsorption in IBS. Overall, there is no clear association between the 2 conditions, with some reports finding no significant difference in the incidence of lactose malabsorption between IBS and control patient groups.[13-15] Conversely, other reports suggest that 40–85% of IBS patients experience a marked improvement in their symptoms following a lactose-restricted diet, suggesting a role for lactose malabsorption in IBS.[4] For example, a prospective uncontrolled study demonstrated that IBS patients with lactose malabsorption experienced significant symptom improvement ($P<.001$) after 6 weeks of a lactose-restricted diet, and a 5-year follow-up found a 75% reduction in outpatient clinic visits by these patients.[16] Because the 2 conditions can coexist, it is important to rule out lactose malabsorption as a cause of some symptoms in IBS patients.

Fructose is another carbohydrate that is poorly absorbed in a number of individuals. In the United States, the consumption of fructose has greatly increased in the general population over the past 2 decades. This change is due, in large part, to the increase of over 1,000% in the consumption of high fructose corn syrup.[17] Several studies have proposed a role for fructose intake and/or fructose intolerance in the development of IBS symptoms.[18,19] However, this theory has not been demonstrated in a prospective controlled setting.[20] A retrospective study of 80 IBS patients found that 38% were fructose-intolerant.[21] This same study reported that a fructose-restricted diet resulted in a significant improvement

(P<.02) in symptoms, including pain, belching, bloating, fullness, indigestion, and diarrhea. However, the noncompliance rate to this diet (46%) was relatively high. Shepherd and colleagues conducted a double-blind, randomized, placebo-controlled trial in which 25 IBS patients who had responded to a change in diet (consisting of food low in free fructose and fructans) were rechallenged by graded-dose introduction of fructose or fructans (alone or in combination) or glucose.[22] A majority of patients rechallenged with fructose, fructans, or the combination reported inadequate control of their IBS symptoms (70%, 77%, and 79%, respectively), all of which were significantly higher than patients rechallenged with glucose alone (14%; P≤.002). Additionally, symptom severity was significantly less for patients rechallenged with glucose. Because fructose intolerance and/or malabsorption can occur simultaneously with IBS, it is recommended that fructose ingestion be restricted over a trial period in IBS patients in order to empirically determine their ability to absorb fructose.[20]

Based upon the mounting evidence of carbohydrate involvement in IBS symptoms, a diet low in carbohydrates has been proposed as a possible intervention for patients with IBS-D.[4] This idea has been initially investigated in a small population of 17 patients with moderate-to-severe IBS-D.[23] These patients received 2 weeks of a standard diet followed by 4 weeks of a very low carbohydrate diet (20 g carbohydrates daily). The shift from the standard to very low carbohydrate diet represented a shift in carbohydrate intake from 55% to 4% of the caloric intake for these individuals. Of the 17 patients, 13 completed the entire study. Importantly, each of these 13 met the response criterion, which was defined as achieving adequate relief of IBS-D symptoms for at least 2 weeks. In fact, 77% reported adequate symptom relief for all 4 weeks of their very low carbohydrate diet. In addition to symptom relief, significant improvements in stool frequency (decrease from 2.6 to 1.4 times per day; P<.001), stool consistency (Bristol stool score decrease from 5.3 to 3.8; P<.001), pain, and quality of life were noted.

Gluten hypersensitivity has also been explored for its importance in IBS. Although the symptoms of celiac disease can mimic IBS, they are distinct conditions. Celiac disease is characterized by a flattened small intestinal mucosa with a lymphocytic infiltrate, crypt hyperplasia, and villous atrophy.[24] The prevalence of celiac disease in the white population overall in the United States is estimated to be 0.5–1%, and some reports suggest that this prevalence is higher in the IBS population.[25-27] Several possibilities could explain this finding, including the misdiagnosis of some celiac disease patients as IBS patients or an association between the 2 diseases; recently, another possibility has also emerged— a gluten sensitivity that is not a true allergy such as that observed in celiac disease.[28] Regardless of the reason, some IBS-D patients experience symptom improvement with the reduction or elimination of gluten from their diet.[29]

Using Probiotics

Experts have varied widely on the definition of probiotics, with no consensus reached as of yet. However, one definition that has been adopted by international health organizations states that probiotics are "live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host."[30] Although probiotics are used by many IBS-D patients, the mechanisms by which probiotics act on intestinal mucosa are not well understood. Some potential mechanisms include growth suppression and inhibition of binding of pathogenic bacteria, improvement of the epithelium barrier function, and alteration of the host's immune activity through a change in the expression profile of inflammatory cytokines.[31,32] Another possibility is the secretion of short chain fatty acids from some probiotics, which results in a decrease in the luminal pH and the expression of bactericidal proteins. Multiple other mechanisms have also been proposed, and it is important to realize that because of our limited understanding of the total flora bacterial population, it is possible that there may be other as-of-yet undefined mechanisms explaining the actions of probiotics.

Probiotics have been studied extensively in IBS. A recent systematic review of 19 randomized controlled trials concluded that, while probiotics conferred a significant benefit in IBS symptoms compared to placebo, the magnitude of this benefit and the preferred species and strains remain to be determined.[33] There are some concerns, and unpublished data, showing that consumers should be cautious, as some probiotics may not be viable when purchased.

One of the initial studies evaluating the benefit of probiotics in IBS was conducted by O'Mahony and colleagues.[32] This study included 77 IBS patients randomized to receive either a probiotic (*Lactobacillus salivarius* UCC4331 or *Bifidobacterium infantis* 35624) or a placebo for 8 weeks. Both probiotic organisms and the placebo were diluted in a malted milk beverage. Compared to placebo, patients randomized to receive *B. infantis* experienced the greatest reduction in score for all symptoms except bowel movement frequency and consistency. This study also found that the IBS patients had an abnormal interleukin (IL)-10:IL-12 ratio, which was indicative of a proinflammatory state. Interestingly, patients treated with *B. infantis* exhibited a normalization in their IL-10:IL-12 ratio.

A subsequent study, conducted by Whorwell and associates, was designed to confirm the beneficial effect of *B. infantis* for IBS patients in the setting of a large multicenter clinical trial.[34] In this study, 362 patients (with either IBS-C or -D) were randomized to receive either placebo or 1 of 3 *B. infantis* dosages over a period of 4 weeks. The primary efficacy endpoint was abdominal pain or discomfort; other endpoints included composite symptom score, global IBS symptom relief, and quality of life. Using these measurements, only 1 *B. infantis* dosage (1×10^8 CFU/mL)
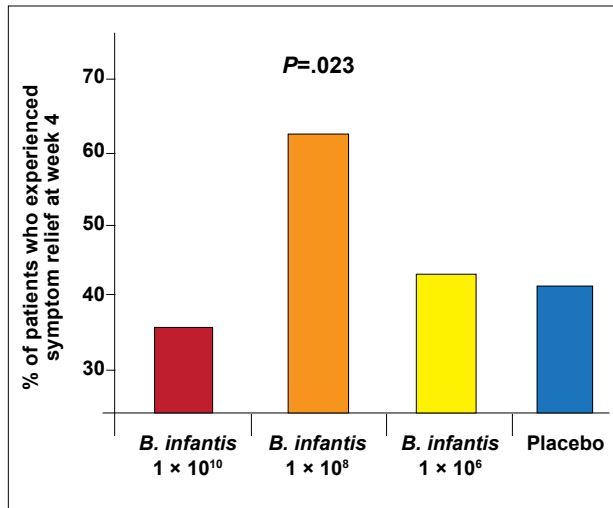
Figure 1. Global assessment of symptom relief in irritable bowel syndrome patients.

Data from Whorwell PJ, et al.[34]

was found to be significantly superior to placebo; the lowest dosage (1×10^6 CFU/mL) did not show significant improvement in symptom relief, and the highest dosage (1×10^{10} CFU/mL) exhibited formulation difficulties (clumping; Figure 1). Stool cultures provided evidence that the administered *B. infantis* actually reached the colon.

Although these 2 studies focused on the beneficial effect of *B. infantis* in IBS, this research does not exclude the possible benefit of other probiotics in this condition. Many questions remain regarding the use of these agents in the management of IBS patients, including the best species, the most beneficial dosages, the possible benefit of combinations of probiotics, and the optimal duration of treatment.

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Using Antibiotics in IBS-D Patients

Brennan M. R. Spiegel, MD, MSHS

A 32-year-old woman with a long-standing history of intermittent abdominal pain and diarrhea was referred to a gastroenterologist due to a worsening of symptoms over the previous 6 months. The patient described her pain as "crampy" and located mainly in the lower left quadrant of her abdomen. Her pain would improve after a bowel movement and then worsen within 10 minutes of eating a meal. Each day, she had up to 6 bowel movements that were generally loose and often urgent. Although her appetite was unaffected, she occasionally skipped eating in order to avoid triggering her symptoms. One of her major complaints involved bloating, which she described as a pressure and fullness in her abdomen, accompanied by visually noticeable abdominal swelling or distention. The patient's bloating episodes were accompanied by a great deal of flatulence that she found to be bothersome and a cause of social awkwardness.

The patient's history was significant for acid reflux disease, for which she was taking a proton pump inhibitor (PPI; omeprazole 20 mg twice daily). She had undergone an appendectomy when she was younger, and her family history was unremarkable. She reported consuming alcohol socially, but not frequently, and had no history of smoking or drug use.

Upon further questioning, it was determined that she had not experienced any recent weight loss, rectal bleeding, fevers, chills, sweats, or vomiting. She had no recent travel history nor had she recently ingested any unusual food items. The patient reported no specific food allergies or intolerance, and she had not been on any antibiotics recently. She had no known allergies to any medications.

The patient's vital signs were unremarkable. Although a physical examination revealed mild tenderness in her lower left abdominal quadrant, she had no evidence of a mass or other abnormality. A rectal examination showed normal function. Prior laboratory tests, including a complete blood cell count, were normal, and a serologic test for celiac disease was negative. Stool studies did not reveal pathogens or the presence of elevated leukocytes.

Prior to this visit to the gastroenterologist, the patient had been diagnosed with IBS by her primary care physician. Although originally prescribed antispasmodic agents, she found them to be largely ineffective drugs that only caused sleepiness. Instead, she intermittently used loperamide to treat flares of fecal urgency and diarrhea, though she had no relief of pain or bloating symptoms. She had also been previously treated with a probiotic, of which she could not recall the name and did not find to be of substantial help. Thus, she was given a referral to the gastroenterologist for further management.

The Role of Small Intestinal Bacterial Overgrowth in IBS-D

The potential role for small intestinal bacterial overgrowth (SIBO) in IBS was popularized nearly 10 years ago after a strong association was discovered between IBS patients and abnormal lactulose hydrogen breath tests. This association was reported by Pimentel and colleagues, who found that 78% of IBS patients had SIBO.[1] This link was subsequently pursued by several groups, some of which found similar results while others were unable to establish the same level of association between the 2 conditions.[2-10]

Because the relationship between SIBO and IBS appears inconsistent among studies, investigators recently published a systematic review and meta-analysis to evaluate the pooled prevalence of SIBO in 12 studies involving 1,921 IBS patients (Figure 2).[11] The pooled prevalence of a positive lactulose hydrogen breath test and glucose breath test in IBS was 54% (95% confidence interval [CI], 32–76%) and 31% (95% CI, 14–50%), respectively. Overall, the pooled odds ratio (OR) for any positive SIBO test in IBS patients compared to healthy controls ranged from 3.45 to 4.7. However, the overall effect did not quite meet the criterion for statistical significance, and there was considerable heterogeneity among the study results. In addition, there was statistical evidence of a possible publication bias, meaning that small, negative studies were missing from the literature.

Regardless of whether the difference in breath test positivity is significantly different between IBS patients and controls, it remains possible that the breath tests are not very accurate in the first place. If this were true, then the data regarding breath test positivity in IBS would become less interpretable. Posserud and associates alternatively used small-bowel aspirates to diagnose SIBO among 162 IBS patients and 26 healthy subjects.[3] Using the standard clinical definition of SIBO ($\geq 1 \times 10^5$ colonic bacteria/mL), its incidence was 4% in both the IBS and healthy groups, suggesting that there was no real clinical association between the 2 conditions. However, when the investigators used a less stringent definition of SIBO reflecting mildly increased bacterial counts ($\geq 5 \times 10^3$ colonic bacteria/mL), a significantly increased incidence was indeed evident among IBS patients compared to controls (43% vs 12%; $P=.002$). This suggests that in some IBS patients, there may be higher-than-normal concentrations of small intestinal bacteria, albeit at lower levels than the traditional threshold for measuring SIBO. It is notable that the traditional threshold is quite arbitrary, so perhaps lower levels remain clinically meaningful.
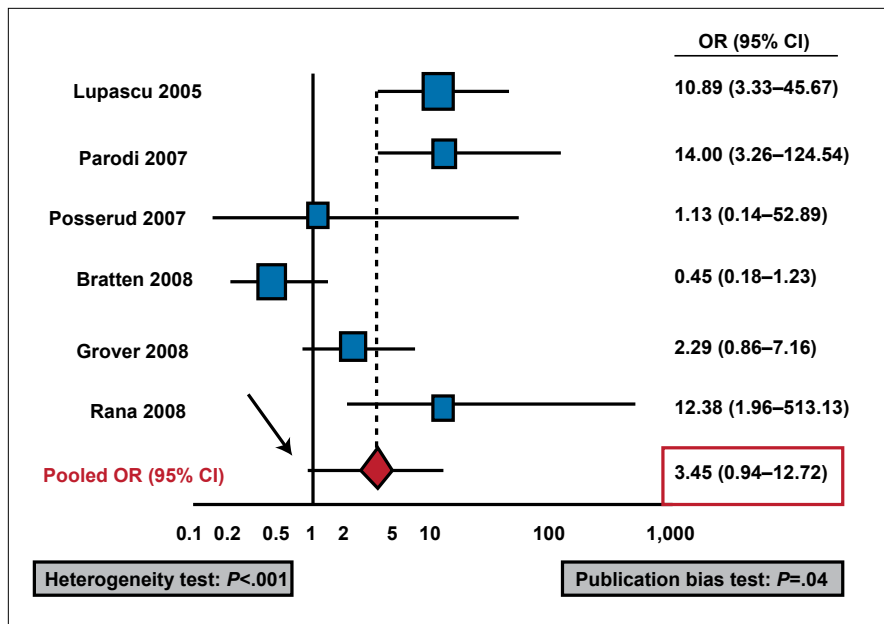
Figure 2. Positive lactulose breath test: odds in irritable bowel syndrome versus controls. The arrow points to the lower bound of the 95% CI, which crosses 1.0; this suggests that the pooled relationship just missed statistical significance in this analysis.

Data from Ford AC, et al.[11]

CI=confidence interval; OR=odds ratio.

Regardless of which threshold we employ to define SIBO, it is reasonable to ask whether SIBO causes IBS symptoms or whether it is possibly an epiphenomenon of a more fundamental, explanatory mechanism. For example, perhaps SIBO occurs because of variations in motility, itself a consequence of something else. Or, perhaps there are abnormalities in mucosal immunity, and SIBO occurs as a consequence of immune dysfunction. If that were true, then SIBO would not necessarily cause IBS, but could be a byproduct of a deeper abnormality.

We have also hypothesized that the relationship between IBS and SIBO could potentially be confounded by the use of PPIs, as follows: PPI therapy in IBS patients is extremely common in everyday clinical practice because IBS patients tend to accumulate PPIs over time; data indicate that even short-term PPI therapy may promote SIBO by eliminating gastric acid, a key antiseptic barrier in the gut; and most existing studies linking SIBO to IBS have not adjusted for or excluded the use of PPI therapy.[12] Linked together, these premises form the basis for a simple hypothesis: the relationship between SIBO and IBS may be confounded by PPIs. In particular, it has long been established that PPI therapy can alter gastric, duodenal, and intestinal bacterial profiles. For example, Thorens and colleagues randomized patients to receive 4 weeks of cimetidine versus omeprazole and, subsequently, they cultured duodenal juice obtained during follow-up endoscopy.[13] The authors found a higher incidence of bacterial overgrowth in the omeprazole arm (53% vs 17%). This finding was duplicated by Fried and associates, who further demonstrated that PPI-related SIBO was due to both oral and colonic-type bacteria, not merely oral flora alone.[14] Theisen and colleagues found that suppression of gastric acid with omeprazole led to a high prevalence of

SIBO that, in turn, led to a markedly increased concentration of unconjugated bile acids.[15] Moreover, Lewis and coworkers documented that omeprazole-related SIBO was associated with shorter intestinal transit times.[16] These latter 2 studies suggest that PPI-related SIBO could potentially lead to symptoms of IBS, such as diarrhea, as a result of an increased osmotic load from bile acids coupled with more rapid intestinal transit. It is notable that the most common side effects of PPIs include abdominal pain, bloating, flatulence, constipation, and diarrhea—symptoms that overlap with IBS. Recently, an Italian group reported nearly twice the incidence of SIBO among patients using PPIs compared to IBS patients (50% vs 24.5%), though the frequency in both of these groups was higher than in healthy controls (6%).[17] Moreover, recent data indicate that, among patients with hydrogen breath test positivity (including patients with IBS) receiving rifaximin for eradication, regrowth of SIBO was independently predicted by the use of concurrent PPI therapy.[18] Thus, not only might PPI therapy lead to SIBO in some patients with IBS, but the recurrence of SIBO following antibiotic therapy might be accelerated in the setting of PPI therapy. In other words, as long as the risk factor for SIBO is present, the condition may recur despite temporary removal with antibiotics. Conversely, Law and Pimentel recently reported that PPI therapy did not significantly alter hydrogen production on lactulose breath tests in IBS patients.[19]

To date, the importance of SIBO in IBS pathogenesis remains unclear. As noted, it is uncertain whether SIBO is central to the pathophysiology of IBS or secondary to another process. There are currently no recommendations guiding clinicians on whether they should routinely test for SIBO in their IBS patients. However, the body of evidence suggests that, particularly for IBS patients with excessive gas

production (manifested as bloating and flatulence), the role of SIBO remains potentially important. Therefore, some of these patients may indeed benefit from appropriate antibiotic interventions to diminish the bacterial overgrowth in their intestines.

Antibiotics for Nonconstipated IBS Patient Management

Clinical trials have provided evidence that antibiotic-mediated reduction or elimination of SIBO can lead to alleviation of IBS symptoms.[20] Some of the earliest studies were double-blind, randomized, placebo-controlled trials that evaluated the antibiotic neomycin. One of these studies reported a 35% improvement in a composite symptom score in patients on neomycin versus only an 11.4% improvement in controls.[21] A second study revealed that 37% of IBS patients achieved global improvement in IBS symptoms with neomycin, compared to only 5% of controls ($P<.001$).[22]

The other major antibiotic that has been evaluated for the treatment of SIBO in IBS patients is rifaximin. This broad-range, nonsystemic oral antibiotic undergoes minimal absorption, thus retaining high concentrations within the gastrointestinal tract.[23] Rifaximin is a promising candidate for the antibiotic treatment of IBS, as it demonstrates no clinically relevant bacterial resistance to date, accumulates in the intestines, and has a favorable toxicity profile. Results in clinical trials demonstrate that rifaximin administration can result in significant improvement in IBS symptoms.[24,25]

Recently, Pimentel and colleagues reported pooled results from 2 phase III clinical trials, the TARGET-1 and TARGET-2 studies.[26] These pooled data consisted of a total of 1,260 nonconstipated IBS patients with mild or moderate symptoms who were randomized to receive 2 weeks of treatment with either rifaximin or placebo. Because the utility of screening for SIBO has yet to be established in IBS patients, the study populations did not undergo routine breath testing. Measurements of efficacy were made over a 4-week period following treatment. Significantly more patients in the rifaximin arms achieved adequate relief of their IBS symptoms compared to the placebo arms (40.7% vs 31.7%; P=.0008), the primary endpoint of the studies. Specifically, more patients treated with rifaximin reported adequate relief of bloating symptoms (40.2% vs 30.3%). Additionally, the responses achieved with rifaximin were found to be durable; symptoms remained significantly improved among rifaximin-treated patients over an additional 6-week follow-up. Secondary endpoints, including stool consistency, abdominal pain, and abdominal discomfort, were all improved with rifaximin treatment compared to placebo. As expected, rifaximin was well tolerated, with an adverse-event profile similar to that of placebo.

Notably, although the pooled results of the TARGET studies demonstrated a significant benefit for rifaximin over placebo, they translated into a number-needed-to-treat (NNT) value of 11. Although this NNT is not unlike the NNTs of other therapies employed in IBS, its significance is amplified by the high cost of the drug. Further research should evaluate the cost-effectiveness of rifaximin, given the NNT of 11 and $20+ daily average wholesale price of therapy.

Overall, these data suggest a role for rifaximin in the treatment of patients with mild-to-moderate IBS without constipation. This may be particularly true for patients who have failed a first-line therapy, who are not on a long-term PPI,[18] or who have failed probiotic therapy.

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Pharmacotherapies for IBS-D

Lin Chang, MD

A 35-year-old white woman initially presented to the gastroenterologist with a history of abdominal and muscular pain following a motor vehicle accident. Her gastrointestinal symptoms included lower abdominal pain, as well as urgency and increased stool frequency, which, at its worst, occurred up to 14 times a day. However, she also reported that her frequency fluctuated from day to day. The patient's stools were generally loose, occasionally watery, and contained mucous. The patient also reported an episode of fecal incontinence associated with diarrhea occurring approximately once a month. Although she previously was employed, the severity of her symptoms currently prevents her from holding a job.

When she first presented to the gastroenterologist, her medications included synthroid and omeprazole. She tried using over-the-counter and prescription antidiarrheal agents, with little relief of her symptoms. She was subsequently prescribed a low dose of amitriptyline, a tricyclic agent, for her bowel symptoms, but the drug caused sedation and a dry mouth.

The patient's history included gastroesophageal reflux disease, Hashimoto thyroiditis, and migraine headaches. She also had a traumatic vaginal delivery that required surgical repair. She had been sexually abused at 14 years of age and had experienced substantive sexual abuse during a 14-year marriage. At the time of her motor vehicle accident, she was under an extreme amount of relationship stress. The patient reported being sober from alcohol for approximately 3 years. Her family history of IBS was negative.

Physical examination revealed essentially normal results, and the patient was noted to be quite slim. Rectal examination was normal, and the patient did not have a tender abdomen at the time. Extensive laboratory tests were performed prior to her referral, all showing negative results. Stool studies were negative, as were celiac serologies and upper endoscopic and colonoscopic examinations (biopsies of the duodenum and colon were reported to be negative). Barium study of the small bowel and abdominal and pelvic CT scans did not reveal any findings. An anorectal manom-etry demonstrated normal anal sphincter pressure at rest but a less-than-25% increase from basal pressure during squeeze command. Rectal sensory thresholds were decreased, which was suggestive of increased rectal perception.

The patient was diagnosed with IBS-D. She was prescribed alosetron when it was initially available in 2000, and she experienced relief of her IBS-D symptoms. However, she had to stop the medication after it was voluntarily withdrawn from the market. She was later restarted on alosetron when it was re-released under the risk management program, and she experienced improvement of her gastrointestinal symptoms.

Targeting the Serotonin Pathway in IBS-D

The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) is well established as an important signaling molecule in normal intestinal function. In the gut, 5-HT activates intrinsic and extrinsic primary afferent neurons, which results in the initiation of peristaltic and secretory reflexes, respectively.[1] 5-HT also acts as a neurotransmitter for the long descending myenteric interneurons. The level of available 5-HT is regulated via serotonin reuptake transporter (SERT)-mediated uptake of 5-HT into enterocytes or neurons. 5-HT has been implicated in multiple gastrointestinal functions, including motility, sensation, blood flow, and secretion.[2-5] 5-HT exerts its diverse actions in the intestines through the binding and activation of multiple 5-HT receptor subtypes.[6]

It has been postulated that altered 5-HT signaling may play a role in the pathogenesis of IBS, and the 5-HT_3 and 5-HT_4 receptors appear to have the most important role in IBS. Although 5-HT_3 signaling is implicated in visceral pain and peristalsis, 5-HT_4 modulates gastric emptying, colonic secretions, the peristaltic reflex, and contraction and relaxation of the intestinal smooth muscle.[4,5,7] Additionally, changes in SERT expression and/or SERT polymorphisms may contribute to altered 5-HT signaling in IBS patients.[8,9]

Because of the importance of 5-HT in normal gastrointestinal function, and due to the potential role of altered 5-HT signaling in IBS pathogenesis, pharmacotherapeutic

targeting of the 5-HT pathway has been explored for IBS treatment. Several targeting strategies have been demonstrated to be effective in this setting, including antagonism and/or activation of the 5-HT$_4$ receptor (primarily using the medication tegaserod) and antagonism of the 5-HT$_3$ receptor (primarily with alosetron).[10]

Alosetron

The selective 5-HT$_3$ receptor antagonist alosetron is currently indicated for the treatment of women with severe IBS-D who have chronic symptoms (≥6 months) of IBS unexplained by anatomic or biochemical gastrointestinal abnormalities and who have not responded adequately to conventional therapy. Several large randomized, controlled trials have shown that alosetron is superior to placebo for relieving abdominal pain and discomfort in women with IBS-D.[11-14] This finding has been demonstrated through the statistically significant decrease in the percentage of days that patients experience a lack of satisfactory control of urgency, as well as an improvement in stool formation and frequency. Additionally, compared to placebo, alosetron therapy is associated with an adequate relief of IBS pain and discomfort (OR, 1.81; 95% CI, 1.57–2.10).[15] Responses to alosetron were generally rapid, with clinically significant improvement in symptoms occurring within 1–4 weeks of initiating treatment. In these studies, mild-to-moderate constipation was the most frequent adverse event.

The use of alosetron to treat IBS-D is complicated by the fact that, although it was originally approved by the US Food and Drug Administration (FDA) in 2000, it was withdrawn from the market later that same year following reports of serious complications of constipation, ischemic colitis, and bowel perforation associated with its use.[16,17] A great deal of pressure was subsequently generated by both clinicians and their IBS patients to bring alosetron back to the market, which led to its reintroduction in 2002. The FDA reapproved the medication with the caveat of using it only under a restricted prescribing program, as well as the implementation of extensive postmarketing studies. Under this program, physicians certify that they are comfortable prescribing alosetron, that they understand the risks and benefits associated with the drug, and that they will discuss these risks and benefits with their patients. The risk evaluation and mitigation strategy was recently approved by the FDA. Among the changes and improvements is the recent replacement of the patient physician agreement (which requires a signature from both parties) with a patient acknowledgment form (which requires only the patient's signature). A 2006 systematic review of clinical trial results and the available postmarket surveillance data reported the rate of ischemic colitis to be very low (1.1 cases per 1,000 patient-years); the cases of ischemic colitis identified in this review were reversible and generally did not result in long-term effects.[16] This review further found that there was no significant increase in

complications due to severe constipation among individuals treated with alosetron compared to placebo. A subsequent 2010 review of safety data from adverse event reporting since the reintroduction of alosetron in 2002 to 2008 demonstrated that the incidence of ischemic colitis and serious complications of constipation were similar to those during the postmarketing cycle before alosetron withdrawal (0.95 and 0.36 cases per 1,000 patient-years, respectively). However, serious outcomes associated with alosetron were mitigated since the reintroduction under the risk management program.[16,18] Thus, while incorporation of alosetron into the management of IBS-D should be considered carefully and only with its approved indication, alosetron appears to be an effective treatment for IBS-D that very rarely results in serious adverse events.

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Question-and-Answer Forum

How can a food intolerance or allergy be established in IBS-D patients?

Dr. Brian E. Lacy IBS patients will often state that a particular food will cause symptoms in one instance but not another, making it difficult to determine whether a true food allergy or intolerance is present. Additionally, the volume of food consumed can affect whether a patient will experience any symptoms. The use of a food diary over a 2- or 3-week period can be a particularly useful strategy to help establish whether a pattern exists between a patient's symptoms and any foods they eat. This is particularly true for IBS-D patients, as their symptoms are often intermittent.

Dr. Brennan M. R. Spiegel Clearly, there is no one diet that can be used for all IBS-D patients. Recommending that patients use a food diary to record their diet over the course of several weeks is an important strategy to help identify any particular dietary restrictions that should be made.

If an IBS-D patient responds to antibiotic therapy, how often are you willing to re-treat them with that antibiotic?

BS This is a difficult question because the evidence supporting long-term antibiotic use in IBS is lacking. The antibiotic rifaximin has not been clinically evaluated as a long-term therapy for IBS-D. The TARGET-1 and TARGET-2 studies investigated a 14-day treatment regimen of rifaximin, with a maximum follow-up of 12 weeks. These trials demonstrated that rifaximin was effective and safe during this time period; however, the performance of rifaximin over a longer time period remains unknown. Also unknown is the ability of rifaximin to be used as a multicourse therapy. I am hesitant to rely upon the long-term use of an antibiotic to treat IBS-D. Some of our IBS patients are young, so the idea of committing them to years of potential antibiotic therapy, even only intermittent courses, gives me great pause.

It is also important to remember that the use of rifaximin does not preclude the inclusion of other therapies into the overall IBS-D patient management strategy.

How should a physician incorporate considerations regarding the cost of rifaximin therapy into decisions for patient management?

BS Compared with most other antibiotics traditionally used for the management of SIBO, the cost of rifaximin treatment is substantially higher—upward of $20 or more per day. Although this high cost may be acceptable over the single 14-day course that has been evaluated in IBS-D, it may prevent physicians and their patients from relying upon it as a long-term or multicycle therapy.

What interventions can be used to treat and/or prevent fecal incontinence in IBS-D patients?

Dr. Lin Chang When IBS patients experience fecal incontinence as one of their symptoms, I believe that their illness should be considered to be more severe, as fecal incontinence is a particularly devastating symptom for patients. When a patient begins to suffer from fecal incontinence, it causes them to constantly be concerned that they will have an episode in public, which is an appropriate and understandable response; even an episode in their home can be disconcerting. Thus, these patients will become particularly vigilant in trying to avoid situations or foods that may trigger an episode, which has the potential to dramatically affect quality of life.

The over-the-counter agent loperamide may be used prophylactically to prevent an episode of fecal incontinence. When patients are experiencing heightened symptoms or a flare, which may result in an episode of fecal incontinence, I advise them to self-administer loperamide 1–2 hours prior to eating a meal or when leaving their home for prolonged periods of time. Often, I will also prescribe a smooth muscle relaxing agent for them to use to decrease postprandial IBS symptoms.

Conclusion

Brian E. Lacy, PhD, MD

IBS-D is a highly prevalent medical disorder that greatly impacts the daily life of patients, generates substantial health-related fears and concerns, and can be challenging to treat. In the absence of warning signs, the diagnosis of IBS-D is typically made at the first office visit, at which time treatment should be initiated. Routine follow-up is recommended 4–6 weeks after the initial office visit, so that response to therapy can be assessed, warning signs reevaluated, and specialized tests scheduled, if necessary. For patients with mild symptoms, treatment can begin with simple dietary interventions such as avoidance of lactose and fructose, as many IBS-D patients suffer from coexisting lactose and/or fructose intolerance. Additionally, some IBS-D patients note a small improvement in symptoms when dietary fiber is restricted. This finding is contrary to traditional thinking regarding fiber and gastrointestinal issues, as it was common practice in the past to recommend the addition of fiber to the diet of IBS-D patients. However, multiple lines of evidence show that excess fiber generally worsens abdominal bloating and distention, which are symptoms typically experienced by IBS-D patients. Overall, the implementation of dietary changes may improve the symptoms of abdominal gas and bloating and may also lessen diarrhea episodes. In addition, although not uniformly successful, these interventions may cause some patients to realize that dietary factors play a role in symptom generation, thus allowing them to avoid those factors. Finally, some IBS-D patients have noted symptom improvement by avoiding gluten, even in the absence of true celiac disease, though there is a lack of data from prospective controlled trials supporting this practice.

As the role of bacteria has been investigated in the etiology of IBS, SIBO has been proposed as having an important role in the natural course of IBS. The occurrence of bacterial overgrowth within the gastrointestinal system would be particularly relevant for IBS-D patients, as it could, in part, explain the symptoms of abdominal bloating, distension, and flatulence experienced due to the production of excess gas. Although SIBO has not been conclusively found to be associated with IBS-D, several clinical trials evaluating bacterial-focused interventions for these patients have met with success. One strategy is to modulate the enteric bacterial population with the administration of probiotics. Probiotics are frequently used by patients to treat IBS-D symptoms because they can be purchased over-the-counter, do not require an office visit, and are reasonably inexpensive. Clinical studies show that one probiotic species,

B. infantis, may improve symptoms of abdominal bloating and pain, though stool frequency and urgency likely will not be changed.[1,2] For many IBS-D patients, stool urgency is one of the most frustrating symptoms, and, thus, most patients will require other therapeutic interventions. Although probiotic therapy appears to be successful in multiple patients, questions remain surrounding its use, including which probiotic species offers the optimal benefit and at what dosage and duration. Another bacterial-focused strategy is the use of antibiotic therapy. Although different antibiotics have been investigated for their activity in IBS, rifaximin has been studied most extensively. Recently reported data from 2 pooled phase III clinical trials demonstrate that rifaximin treatment leads to significant symptom improvement compared to placebo, a finding that supports a role for rifaximin in IBS-D therapy.[3] However, the routine incorporation of rifaximin in IBS treatment strategies may be limited by its high cost.

Despite dietary and bacterial-focused interventions, most IBS-D patients suffer from persistent symptoms of diarrhea and abdominal pain. These symptoms prompt many clinicians to initiate treatment with either loperamide or diphenoxylate-atropine. Loperamide is a synthetic phenylpiperidine derivative approved by the FDA in 1976 for the treatment of diarrhea. Structurally similar to meperidine, loperamide has minimal analgesic activity and does not produce euphoria at standard doses. Loperamide inhibits intestinal secretion and peristalsis and slows intestinal transit, thus improving fluid absorption and symptoms of diarrhea. Four studies have evaluated the efficacy of loperamide for the treatment of patients with IBS and diarrhea.[4-7] In general, these studies demonstrated that stool frequency was reduced and stool consistency improved in patients treated with loperamide compared to placebo. However, abdominal pain was not improved, and in some patients, abdominal pain worsened during the nocturnal period. In addition, symptoms of bloating did not improve. Surprisingly, no randomized, placebo-controlled trials using diphenoxylate-atropine have been performed in patients with IBS-D; thus, a formal recommendation cannot be made. Clinical experience suggests that diphenoxylate-atropine may improve symptoms of diarrhea in patients with IBS-D but will not improve symptoms of abdominal pain or bloating.

Patients who fail these interventions (dietary modulation, probiotic and/or antibiotic therapy, and/or loperamide or diphenoxylate-atropine) are often told that there are no

other options for treating their persistent symptoms. This large patient population should be appropriately categorized as having severe IBS-D, as they have failed conventional therapy. In fact, the FDA has stated that to be categorized as a "severe" IBS-D patient, women must meet only 1 of the following 3 criteria: frequent and severe abdominal pain/discomfort; frequent bowel urgency or fecal incontinence; or disability or restriction of daily activities due to IBS. For these women, alosetron, a 5-HT_3 receptor antagonist, is a reasonable treatment option. In fact, if one were to use evidence-based guidelines with the objective of improving global IBS symptoms, alosetron would be a logical choice.[8] Alosetron treatment is associated with slowed colonic transit, enhanced small intestine fluid reabsorption, and improved visceral pain. A recent systematic review and meta-analysis of 8 randomized controlled trials involving 4,842 patients determined that alosetron provided a significant reduction in the global symptoms of diarrhea, abdominal pain, and bloating in patients with IBS-D.[9] Alosetron is currently the only medication approved by the FDA for the treatment of IBS-D (in women only). Some clinicians have been wary about administering alosetron due to the potential risk of developing constipation, which is a predictable physiologic adverse event based upon the mechanism of action of the medication. In addition, other physicians are concerned by the theoretical risk of patients developing ischemic colitis. For these reasons, a risk management plan was instituted when alosetron was returned to the US market. Since the introduction of this risk management plan, the number of adverse events has declined, and the rate of ischemic colitis was recently calculated at 0.95 per 1,000 patient-years, whereas the rate of serious complications of constipation was found to be 0.36 per 1,000 patient-years.[10] Interestingly, since the initial reports of adverse events associated with alosetron were published, research has shown that all patients with IBS have a 2–4-fold increased risk of ischemic colitis compared to the general population.[11] It is quite possible that some of the initial adverse events attributed to alosetron were, in fact, due to the underlying disorder and not the medication.

Management of IBS-D patients is an issue requiring continual education for clinicians, particularly as advancements are made in the understanding of the pathophysiology and the natural course of the disease. Although official guidelines and recommendations regarding IBS-D treatment are limited, careful review of the existing literature provides a basis for physicians to implement therapeutic strategies in their patients, with the goals of alleviating symptoms and improving quality of life.
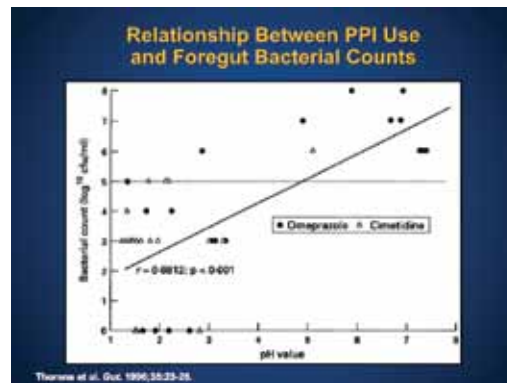
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