

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.

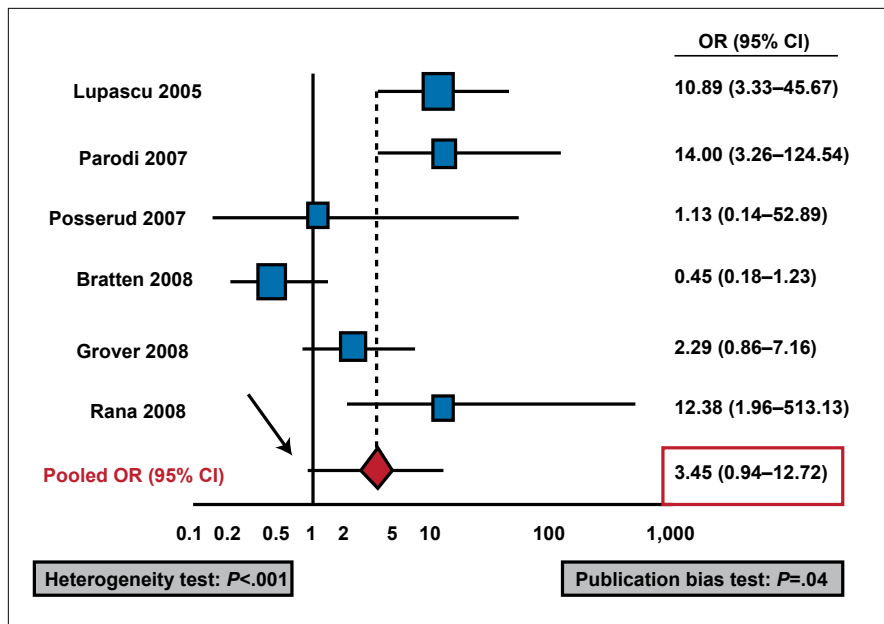


Figure 2. Positive lactulose breath test: odds in irritable bowel syndrome versus controls. The arrow points to the lower bound of the 95% CI, which crosses 1.0; this suggests that the pooled relationship just missed statistical significance in this analysis.

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.

References

- Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol*. 2000;95:3503-3506.
- Cuoco L, Salvagnini M. Small intestine bacterial overgrowth in irritable bowel syndrome: a retrospective study with rifaximin. *Minerva Gastroenterol Dietol*. 2006;52:89-95.
- Posserud I, Stotzer PO, Björnsson ES, Abrahamsson H, Simren M. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. *Gut*. 2007;56:802-808.
- Weinstock LB, Klutke CG, Lin HC. Small intestinal bacterial overgrowth in patients with interstitial cystitis and gastrointestinal symptoms. *Dig Dis Sci*. 2008;53:1246-1251.
- Majewski M, McCallum RW. Results of small intestinal bacterial overgrowth testing in irritable bowel syndrome patients: clinical profiles and effects of antibiotic trial. *Adv Med Sci*. 2007;52:139-142.
- Carrara M, Desideri S, Azzurro M, et al. Small intestine bacterial overgrowth in patients with irritable bowel syndrome. *Eur Rev Med Pharmacol Sci*. 2008;12:197-202.
- Pimentel M. The prevalence of small intestinal bacterial overgrowth in irritable bowel syndrome: IBS vs healthy controls (not historical definitions). *Gut*. 2008;57:1334-1335; author reply 1335.
- Peralta S, Cottone C, Doveri T, Almasio PL, Craxi A. Small intestine bacterial overgrowth and irritable bowel syndrome-related symptoms: experience with rifaximin. *World J Gastroenterol*. 2009;15:2628-2631.
- Parodi A, Dulbecco P, Savarino E, et al. Positive glucose breath testing is more prevalent in patients with IBS-like symptoms compared with controls of similar age and gender distribution. *J Clin Gastroenterol*. 2009;43:962-966.
- Ghoshal UC, Kumar S, Mehrotra M, Lakshmi C, Misra A. Frequency of small intestinal bacterial overgrowth in patients with irritable bowel syndrome and chronic non-specific diarrhea. *J Neurogastroenterol Motil*. 2010;16:40-46.
- Ford AC, Spiegel BM, Talley NJ, Moayyedi P. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2009;7:1279-1286.
- Spiegel BM, Chey WD, Chang L. Bacterial overgrowth and irritable bowel syndrome: unifying hypothesis or a spurious consequence of proton pump inhibitors? *Am J Gastroenterol*. 2008;103:2972-2976.
- Thorens J, Froehlich F, Schwizer W, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. *Gut*. 1996;39:54-59.
- Fried M, Siegrist H, Frei R, et al. Duodenal bacterial overgrowth during treatment in outpatients with omeprazole. *Gut*. 1994;35:23-26.
- Theisen J, Nehra D, Citron D, et al. Suppression of gastric acid secretion in patients with gastroesophageal reflux disease results in gastric bacterial overgrowth and deconjugation of bile acids. *J Gastrointest Surg*. 2000;4:50-54.
- Lewis SJ, Franco S, Young G, O'Keefe SJ. Altered bowel function and duodenal bacterial overgrowth in patients treated with omeprazole. *Aliment Pharmacol Ther*. 1996;10:557-561.
- Lombardo L, Foti M, Ruggia O, Chiechio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. *Clin Gastroenterol Hepatol*. 2010;8:504-508.
- Lauritano EC, Gabrielli M, Scarpellini E, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. *Am J Gastroenterol*. 2008;103:2031-2035.
- Law D, Pimentel M. Proton pump inhibitor therapy does not affect hydrogen production on lactulose breath test in subjects with IBS. *Dig Dis Sci*. 2010;55:2302-2308.
- Frissora CL, Cash BD. Review article: the role of antibiotics vs. conventional pharmacotherapy in treating symptoms of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2007;25:1271-1281.

21. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. A double-blind, randomized, placebo-controlled study. *Am J Gastroenterol*. 2003;98:412-419.
22. Pimentel M, Chatterjee S, Chow EJ, Park S, Kong Y. Neomycin improves constipation-predominant irritable bowel syndrome in a fashion that is dependent on the presence of methane gas: subanalysis of a double-blind randomized controlled study. *Dig Dis Sci*. 2006;51:1297-1301.
23. Pimentel M. Review of rifaximin as treatment for SIBO and IBS. *Expert Opin Investig Drugs*. 2009;18:349-358.
24. Pimentel M, Park S, Mirocha J, Kane SV, Kong Y. The effect of a nonabsorbed

- oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med*. 2006;145:557-563.
25. Sharara AI, Aoun E, Abdul-Baki H, Mounzer R, Sidani S, Elhajj I. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. *Am J Gastroenterol*. 2006;101:326-333.
26. Pimentel M, Lembo A, Chey WD, et al. Rifaximin treatment for 2 weeks provides acute and sustained relief over 12 weeks of IBS symptoms in non-constipated irritable bowel syndrome: results from 2 North American phase 3 trials (Target 1 and Target 2). Presented at Digestive Disease Week. May 1-5, 2010. New Orleans, Louisiana. Abstract 475i.

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-HT₃ and 5-HT₄ receptors appear to have the most important role in IBS. Although 5-HT₃ signaling is implicated in visceral pain and peristalsis, 5-HT₄ 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-HT₄ receptor (primarily using the medication tegaserod) and antagonism of the 5-HT₃ receptor (primarily with alosetron).¹⁰

Alosetron

The selective 5-HT₃ 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.

References

- Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. *Gastroenterology*. 2007;132:397-414.
- Crowell MD. Role of serotonin in the pathophysiology of the irritable bowel syndrome. *Br J Pharmacol*. 2004;141:1285-1293.
- Greenwood-van Meerveld B. Importance of 5-hydroxytryptamine receptors on intestinal afferents in the regulation of visceral sensitivity. *Neurogastroenterol Motil*. 2007;(19 suppl 2):13-18.
- Gershon MD. Review article: serotonin receptors and transporters—roles in normal and abnormal gastrointestinal motility. *Aliment Pharmacol Ther*. 2004;(20 suppl 7):3-14.
- Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther*. 1999;(13 suppl 2):15-30.
- Sikander A, Rana SV, Prasad KK. Role of serotonin in gastrointestinal motility and irritable bowel syndrome. *Clin Chim Acta*. 2009;403:47-55.
- Taniyama K, Makimoto N, Furuichi A, et al. Functions of peripheral 5-hydroxytryptamine receptors, especially 5-hydroxytryptamine₄ receptor, in gastrointestinal motility. *J Gastroenterol*. 2000;35:575-582.
- Coates MD, Mahoney CR, Linden DR, et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. *Gastroenterology*. 2004;126:1657-1664.
- Yeo A, Boyd P, Lumsden S, et al. Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut*. 2004;53:1452-1458.
- Hammerle CW, Surawicz CM. Updates on treatment of irritable bowel syndrome. *World J Gastroenterol*. 2008;14:2639-2649.
- Lembo T, Wright RA, Bagby B, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol*. 2001;96:2662-2670.
- Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch Intern Med*. 2001;161:1733-1740.
- Camilleri M, Mayer EA, Drossman DA, et al. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT₃ receptor antagonist. *Aliment Pharmacol Ther*. 1999;13:1149-1159.
- Camilleri M, Northcutt AR, Kong S, Dukas GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomized, placebo-controlled trial. *Lancet*. 2000;355:1035-1040.
- Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Neurogastroenterol Motil*. 2003;15:79-86.
- Chang L, Chey WD, Harris L, Olden K, Surawicz C, Schoenfeld P. Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. *Am J Gastroenterol*. 2006;101:1069-1079.
- Horton R. Lotronex and the FDA: a fatal erosion of integrity. *Lancet*. 2001;357:1544-1545.
- Chang L, Tong K, Ameen V. Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. *Am J Gastroenterol*. 2010;105:866-875.

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 multicourse 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 piperidine 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-HT₃ 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.

References

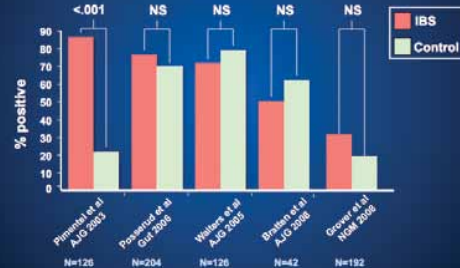
1. O'Mahony L, McCarthy J, Kelly P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005;128:541-551.
2. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. *Am J Gastroenterol*. 2006;101:1581-1590.
3. Pimentel M, Lembo A, Chey WD, et al. Rifaximin treatment for 2 weeks provides acute and sustained relief over 12 weeks of IBS symptoms in non-constipated irritable bowel syndrome: results from 2 North American phase 3 trials (Target 1 and Target 2). Presented at Digestive Disease Week. May 1–5, 2010. New Orleans, Louisiana. Abstract 475i.
4. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci*. 1984;29:239-247.
5. Efskind PS, Bernklev T, Vatn MH. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. *Scand J Gastroenterol*. 1996;31:463-468.
6. Hovdenak N. Loperamide treatment of the irritable bowel syndrome. *Scand J Gastroenterol Suppl*. 1987;130:81-84.
7. Lavo B, Stenstam M, Nielsen AL. Loperamide in treatment of irritable bowel syndrome—a double-blind placebo controlled study. *Scand J Gastroenterol Suppl*. 1987;130:77-80.
8. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104(suppl 1):S1-35.
9. Ford A, Brandt L, Foxx-Orenstein A, et al. Efficacy of 5HT₃-antagonists in non-constipation predominant irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol*. 2008;103:S477.
10. Chang L, Tong K, Ameen V. Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. *Am J Gastroenterol*. 2010;105:866-875.
11. Higgins PD, Davis KJ, Laine L. Systematic review: the epidemiology of ischaemic colitis. *Aliment Pharmacol Ther*. 2004;19:729-738.

Slide Library

Probiotics in Irritable Bowel Syndrome

- Whorwell et al (*Am J Gastroenterol.* 2006)
- Bifidobacterium infantis* 35624
- Dose – 1 x 10⁹, 10⁸, 10¹⁰ CFU/mL daily x 4 weeks
- Route – freeze-dried, encapsulated
- Randomized, double-blinded, PC; multicenter
- Rome II criteria – all subtypes (55% IBS-D; 21% IBS-C)
- 362 female IBS patients (approximately 90 per group); 330 completed the study; 293 analyzed
- Primary endpoint – abdominal pain score (6 point Likert scale); global IBS symptoms

IBS Versus Controls: H₂ Rise >20 ppm by 180

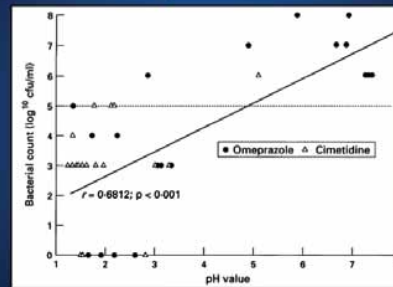


SIBO Recurrence Following Rifaximin



Lauritano et al. *Am J Gastroenterol.* 2008;103:2031-2035.

Relationship Between PPI Use and Foregut Bacterial Counts



Thorrens et al. *Gut.* 1996;35:23-28.

5HT₃ Antagonists: Alosetron

- Clinical Trial Results**
 - 8 studies, 4,967 patients
 - RR symptom remain = 0.79 (95% CI, 0.69–0.90)
 - NNT = 8 (95% CI, 5–17)
- Indication: women with severe IBS-D**
- What really helps**
 - Start with 0.5 mg bid
 - Teach patient to titrate dose to avoid constipation and relieve pain and diarrhea
 - Monitor for constipation and ischemic colitis

Ford AC et al. *Am J Gastroenterol.* 2009;104:1831-1834.

Incidence Rates of IC and CoC During Postmarketing Surveillance: Before/After Reintroduction (up to June 2008)

| | Before June 2002 (prior to withdrawal) | November 2002–June 2008 (after reintroduction) |
|--------------------------------------|--|--|
| Number of Patients | 316,882 | 29,072 |
| Number of Prescriptions | 586,000 | 203,939 |
| Patient-Years | 48,829 | 16,762 |
| Ischemic Colitis | | |
| Probable/possible (n=16) | 0.96 | 0.95 |
| All Cases (n=21) | 1.7 | 1.25 |
| Complications of Constipation | | |
| Confirmed by HCPs (n=6) | 0.59 | 0.36 |
| All Cases (n=16) | 2.0 | 0.95 |

Cheng L, Tong K, Ameen V. *Am J Gastroenterol.* 2010;105:868-875.

For a free electronic download of these slides, please direct your browser to the following web address:
http://www.clinicaladvances.com/index.php/our_publications/gastro_hep-issue/gh_september_2010/

