Irritable Bowel Syndrome: Emergence of New Diagnostic and Treatment Options

Leonard B. Weinstock, MD

Associate Professor of Clinical Medicine and Surgery
Washington University School of Medicine, St Louis, Missouri

ABSTRACT

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by alterations in bowel function (diarrhea and/or constipation) and symptoms of abdominal pain. Symptom-based classifications, including the Rome criteria, are an important foundation for identifying IBS but are not definitive diagnostic tools. Recent understanding of IBS pathophysiology promises to yield novel diagnostic techniques that may supplement the symptom-based approaches as well as new pharmacologic agents and nontraditional therapies that address the underlying causes of IBS. Although therapeutic relief of symptoms remains the primary goal of IBS management, diagnostic and treatment options for IBS will continue to evolve with further understanding of the disorder, and new IBS therapies will likely expand beyond mere management of clinical symptoms. This article briefly reviews the symptom-based diagnostic criteria, discusses emerging diagnostic techniques, and highlights new pharmacologic therapies currently being evaluated for treatment of IBS.

INTRODUCTION

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

The diagnosis of IBS is primarily based on clinical symptoms and the exclusion of other conditions (eg, inflammatory bowel disease [IBD], celiac disease, colorectal cancer, lactose intolerance).[5-7] Although no single biologic marker exists to reliably identify patients with IBS,[5] the emergence of new diagnostic techniques, such as lactulose breath testing, offers options for clinicians. As the understanding of IBS and diagnostic methods progresses, new testing procedures will most likely complement, rather than replace, existing symptom-based diagnostic criteria.

Similarly, treatment options for IBS have traditionally focused on symptomatic relief of abdominal pain, diarrhea, and constipation,[8] but as understanding of the disease etiology progresses, new pharmacologic agents will address the underlying causes of IBS and deliver targeted therapy. This review article summarizes the symptomatic diagnostic criteria and treatment options for IBS and highlights new diagnostic methods and therapies showing potential benefit in the management of the disorder.

SYMPTOM-BASED DIAGNOSIS OF IBS

Methodologies for diagnosing IBS have evolved since the 1970s, with the most extensively evaluated symptom-based criteria being the Manning criteria.[5, 6] These criteria consist of 6 symptoms that differentiate IBS from other GI disorders (Table 1)[9] and are associated with a positive predictive value of 65% to 75%.[5] Building on the Manning criteria, the Rome diagnostic criteria were developed by expert consensus and have been periodically revised.[1, 7, 10] The most recent version (Rome III) is designed to build on the clinical relevance of the initial criteria and includes 3 clinical observations that, when coincident with the recurrence of abdominal pain or discomfort, are associated with a diagnosis of IBS (Table 1).[1] While symptom-based diagnostic criteria for IBS, combined with tests to exclude alternative diagnoses, continue to have clinical value, the development of additional diagnostic methods (eg, identification of specific biomarkers associated with IBS) may allow clinicians to identify patients with IBS more accurately.

EMERGING DIAGNOSTIC TESTING

Small Intestinal Bacterial Overgrowth and Breath Testing

Small intestinal bacterial overgrowth (SIBO), a condition in which abnormally high concentrations of enteric bacteria are present in the small intestine, has been reported in as many as 84% of patients meeting diagnostic criteria for IBS.[11, 12] The onset of SIBO may be the result of poor clearance of intestinal contents caused by altered intestinal motility and includes symptoms similar to those associated with IBS.[13] The most common indirect method for diagnosing SIBO is breath testing. Bacterial overgrowth results in an increased concentration of hydrogen and/or methane in exhaled breath due to malabsorption of the carbohydrate and thus, more carbohydrate being available for bacterial fermentation. The breath test measures the amount of these gases and enables SIBO diagnosis. Several different carbohydrates may be administered, including glucose, lactulose, lactose, fructose, xylose, and sorbitol, with lactulose being the most common. The lactulose breath test (LBT) may prove beneficial in diagnosing specific subtypes of IBS.

Several studies have shown correlations between SIBO (as diagnosed via LBT) and IBS. One prospective study demonstrated that 78% of patients who met Rome I criteria also had SIBO, as confirmed by hydrogen-positive LBT results.[11] A similar study found that 17% of patients with IBS demonstrated methane-positive LBT results compared with only 3% of patients with IBD. [14] A placebo-controlled study demonstrated that 84% of patients with IBS displayed hydrogen- or methane-positive LBT results at baseline.[12] To add to this, an observational study of 254 patients with IBS found that 47% had elevated hydrogen levels, 11% had elevated methane levels, and 6% had elevated levels of both gases.[15]

The results of these studies support the association between SIBO and IBS and the administration of the LBT in IBS diagnosis; however, further investigation is required before LBT can be used in clinical practice, as not all data support the prevalence of SIBO in patients with IBS. For example, a study evaluating hydrogen breath testing employing lactulose and xylose as substrates in individuals with IBS demonstrated that the majority did not have bacterial overgrowth, reporting only 10% with abnormal lactulose breath test results and 13% with abnormal xylose breath test results.[16] In a systematic review evaluating the validity of diagnostic techniques for SIBO, only 33 out of 71 clinical studies attempted to validate breath-testing methods with a traditional “gold standard” method (eg, jejunal culture, ^{14}C-xylose breath test).[17] However, substantial

heterogeneity was observed in these studies, primarily because of the inconsistency in definitions used for a positive breath test and the high variability of breath-testing frequencies.

Standardized interpretation of breath test results remains to be implemented into clinical practice. Additionally, certain tests may produce false results. Because lactulose is not absorbed in the GI tract, LBT results may reflect the activity of bacteria throughout the entire GI tract and not necessarily overgrowth in the small intestine. Alternatively, glucose is normally absorbed by the proximal small intestine; therefore, overgrowth in the distal small intestine may remain undetected by glucose breath testing. Thus, the choice of carbohydrates employed in breath testing reflects a potential trade-off between diagnostic sensitivity and specificity. Overall, no effectively validated diagnostic test for SIBO has been identified, emphasizing the need for a more accurate, reliable method for identifying bacterial overgrowth in patients with IBS.

Other Diagnostic Biomarkers

The identification of consistent biomarkers for IBS may also improve diagnostic methods by making blood and urine tests possible. While no such tests have been validated in controlled trials or applied in clinical practice, biochemical studies have evaluated patients with IBS and demonstrated alterations of the hypothalamic-pituitary–adrenal axis, an important link between the brain and GI tract.[18] Clinical studies have demonstrated an increased number of inflammatory cytokines and activated mast cells in intestinal and colonic biopsies of patients with IBS, and data show that indicators of intestinal permeability may serve as important diagnostic biomarkers.[19, 20] Another diagnostic possibility may be the measurement of neurotransmitters. A separate preliminary study recorded elevated urinary levels of 5-hydroxyindole acetic acid (P=0.036) and plasma levels of nitric oxide (P=0.019) in patients with IBS-D.[21] Further understanding of these underlying causes of IBS may allow for new diagnostic possibilities.

CURRENT TREATMENT OPTIONS FOR IBS

Further understanding of the pathophysiology of IBS may contribute to the development of more effective treatment options. Nonpharmacologic treatment options include diet modification, exercise, and stress reduction. Increasing dietary fiber is often recommended to patients with IBS, but the overall efficacy of fiber in relieving GI symptoms is unclear.[22] Dietary restrictions are often implemented, as a number of patients with IBS have sensitivity to certain trigger foods (eg, gluten, caffeine). Pharmacologic therapies have traditionally focused on the relief of IBS symptoms,[8, 22] but new therapies that target potential underlying causes of IBS are being evaluated.

Pharmacologic Therapies

A variety of pharmacologic agents are currently administered to relieve symptoms of abdominal pain, diarrhea, and constipation in patients with IBS (Table 2). However, their use and efficacy are limited. For example, antispasmodic agents, such as dicyclomine and hyoscyamine, relax GI muscle tension and help relieve abdominal pain temporarily,[23, 24] but their overall benefit remains unclear.[8] Similarly, polyethylene glycol increases stool frequency in patients with possible IBS-C, but its efficacy in relieving pain and other GI symptoms has yet to be determined.[8, 25] In addition, loperamide, an opioid receptor agonist, is effective in reducing incidence of diarrhea in IBS but does not relieve abdominal pain or distention.[26]

Other treatment options include modulators of serotonin receptors, such as alosetron and tegaserod, which help improve intestinal motility and relieve symptoms of IBS. Alosetron improves diarrheal symptoms, including stool frequency and consistency[27-31]; however, it is only indicated for female patients with severe IBS-D who have not responded to conventional therapy[32] and may cause constipation or serious GI adverse events, including ischemic colitis. Similarly, administration of tegaserod increases global relief of IBS symptoms, specifically constipation, in patients with IBS-C. However, in early 2007, tegaserod was removed from the market by the US Food and Drug Administration (FDA) because of the potential increased risk of chest pain, heart attack, and stroke.[33] In 2008, Novartis indicated that tegaserod would only be available in emergency situations and must be requested through the US FDA.

Antidepressants may be prescribed because of the potential to alter GI motility and treat coexisting psychologic conditions in patients with IBS.[34] Of these, tricyclic antidepressants (TCAs) are the most widely studied, with >85% of patients with IBS achieving at least a moderate clinical response;[35] this response was not dependent on changes in psychologic symptoms (eg, anxiety, depression).[34] Contemporary antidepressants (ie, selective serotonin reuptake inhibitors [SSRIs]) have not proven as effective as TCAs for treatment of IBS. They have a slow onset of action, require higher dosing concentrations, and act by reducing anxiety and depression, but do not alleviate specific IBS symptoms[35]; however, only 1 randomized, placebo-controlled trial has directly compared the efficacy of a TCA with an SSRI for treatment of IBS.[36] In this study, patients with IBS based on Rome II criteria received 12 weeks of treatment with the TCA imipramine (50 mg; n=18), the SSRI citalopram (40 mg; n=17), or placebo (n=16) and were asked weekly yes/no questions regarding adequate relief of global IBS symptoms. Treatment with imipramine or citalopram did not substantially improve global symptoms of IBS versus placebo, although imipramine provided greater relief of psychologic symptoms associated with IBS.[36] Overall, pharmacologic therapies may be useful; however, physicians must take into consideration adverse events associated with various treatment regimens.

Antibiotics

Given the potential association between SIBO and IBS, the clinical benefit of antibiotics in patients with IBS has been investigated. Several antibiotics have been shown to be useful in treating SIBO, including amoxicillin-clavulanic acid, ciprofloxacin, and doxycycline.[37] However, though initially effective, these treatments may not be beneficial long-term because of the development of bacterial resistance and other adverse events.[37] In contrast, the antibiotic neomycin has been shown to be effective in IBS in 2 clinical studies. One study showed that 50% of patients with IBS who received neomycin 1000 mg/d for 10 days achieved a 35% reduction in severity of IBS symptoms.[12] A subsequent study reported that among patients with IBS-C, 19 who received neomycin 1000 mg/d for 10 days achieved a mean global improvement of 37% in IBS symptoms from baseline compared with a 5% improvement for those who received placebo (P<0.001).[38] Though these studies suggest that neomycin provides relief of IBS symptoms, it is associated with serious adverse events, including renal toxicity and ototoxicity. Because of this, and the threat of bacterial resistance, other antibiotics, such as rifaximin, are being evaluated for use.

Rifaximin is a nonsystemic antibiotic with broad-spectrum antibacterial activity against enteric pathogens[39] that has shown efficacy in the treatment of SIBO[40-45] and IBS.[15, 37, 42-44, 46-48] Rifaximin has minimal bioavailability (<0.4%) that concentrates its

activity in the GI tract and reduces the potential occurrence of systemic adverse events and drug-drug interactions.[39, 49-51] According to a retrospective chart review by Yang et al,[37] 69% of patients receiving rifaximin experienced clinical response compared with 38% of patients receiving neomycin and 44% of patients receiving other antibiotics (eg, amoxicillin/clavulanate potassium, doxycycline; *P*<0.01). Rifaximin may also be superior to traditional antibiotics in maintain remission from IBS symptoms. In a randomized, double-blind, placebo-controlled trial, 41% of patients with IBS treated with rifaximin achieved global symptomatic response and, 10 days posttreatment, 27% of this group maintained remission. This was in comparison to patients receiving placebo, of which only 23% achieved global symptomatic response. At 10 days posttreatment, only 12% of placebo patients maintained remission of their IBS symptoms. (Fig. 1)[48] In a second randomized, double-blind, placebo-controlled trial, patients (n=43) with IBS who received rifaximin 1200 mg/d for 10 days experienced a 36% mean improvement from baseline in the severity of IBS symptoms at 10 weeks posttreatment, compared with a mean improvement of 21% among 44 patients who received placebo (*P*=0.02; Fig. 2).[47] The positive results of the aforementioned trials support antibiotic therapy as a clinically useful treatment option in IBS and warrant further investigation into the clinical benefit of nonsystemic antibiotics in patients with IBS.

Probiotics

There is increasing interest in administering probiotics to treat IBS, although studies differ as to the reported effectiveness of these agents.[52] For example, a small, placebo-controlled, 8-week study of probiotic mixture VSL #3 demonstrated no significant benefit over placebo in relieving GI symptoms in patients with IBS-D (N=25),[53] while 2 other studies examining the effectiveness of different probiotic mixtures on IBS symptoms found that patients treated with the mixtures had reduced symptom severity (n=41)[54] and overall composite IBS (n=43) score compared with placebo.[55] Single probiotics may also be administered with positive results as shown in 2 recent clinical trials. Whorwell et al[56] found that female patients treated with *Bifidobacterium infantis* 35624 experienced significant relief from baseline GI symptoms compared with controls. A study by Guyonnet et al[57] showed increased stool frequency in patients with IBS-C following administration of fermented milk containing the probiotic *B animalis* DN-173 010. Overall, results from these studies suggest that certain probiotic agents may normalize bacterial concentrations in the bowel and help relieve symptoms of IBS.

SUMMARY

Irritable bowel syndrome is a major health problem, and its unknown etiology has traditionally limited diagnostic and treatment techniques. Symptom-based classifications, including the Manning and Rome criteria, are an important foundation for identifying IBS but are not definitive diagnostic tools. Increased understanding of IBS pathophysiology and the identification of factors most likely to influence its onset (eg, SIBO and inflammation) are essential for expanding diagnostic and treatment methodologies. In the absence of a reliable biomarker to identify IBS, diagnostic methods such as breath testing appear promising but require further investigation to determine their practical utility in the clinical setting.

Treatment of IBS has traditionally addressed the GI symptoms of the disorder (notably constipation, diarrhea, and abdominal pain), and while symptomatic relief will remain the principal goal of treatment, new therapies that target the underlying causes of IBS may provide long-term benefit for patients with IBS. The efficacy and safety of several agents are currently being investigated, but the association between SIBO and IBS suggests that antibiotic and probiotic therapy offer particular promise in disease management. Notably, the nonsystemic antibiotic rifaximin has demonstrated efficacy in improving IBS symptoms, and its favorable safety profile warrants consideration as an addition to the IBS pharmacopoeia.

WORD COUNT: 2462
WORD LIMIT: 2500

FIGURE LEGENDS

FIGURE 1. Proportion of patients with irritable bowel syndrome who received rifaximin 800 mg/d (n=37) or placebo (n=33) who achieved symptomatic response after 10 days of treatment and at 10 days posttreatment. *$P \leq 0.05$ vs placebo.[48]

FIGURE 2. Mean improvement from baseline in symptom severity after 10 weeks posttreatment among patients with irritable bowel syndrome who received rifaximin 1200 mg/d (n=43) or placebo (n=44) for 10 days. *$P = 0.02$ vs placebo.[47]

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology.* Apr 2006;130(5):1480-1491.

2. Hungin AP, Chang L, Locke GR, Dennis EH, Barghout V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. *Aliment Pharmacol Ther.* Jun 1 2005;21(11):1365-1375.

3. Saito YA, Schoenfeld P, Locke GR, 3rd. The epidemiology of irritable bowel syndrome in North America: a systematic review. *Am J Gastroenterol.* Aug 2002;97(8):1910-1915.

4. Martin BC, Ganguly R, Pannicker S, Frech F, Barghout V. Utilization patterns and net direct medical cost to Medicaid of irritable bowel syndrome. *Curr Med Res Opin.* 2003;19(8):771-780.

5. Cash BD, Chey WD. Diagnosis of irritable bowel syndrome. *Gastroenterol Clin North Am.* Jun 2005;34(2):205-220, vi.

6. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. *Am J Gastroenterol.* Nov 2002;97(11):2812-2819.

7. Thompson WG. The road to Rome. *Gastroenterology.* Apr 2006;130(5):1552-1556.

8. Chang HY, Kelly EC, Lembo AJ. Current gut-directed therapies for irritable bowel syndrome. *Curr Treat Options Gastroenterol.* Jul 2006;9(4):314-323.

9. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *Br Med J.* Sep 2 1978;2(6138):653-654.

10. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut.* Sep 1999;45 Suppl 2:II43-47.

11. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol.* Dec 2000;95(12):3503-3506.

12. 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.* Feb 2003;98(2):412-419.

13. Pimentel M, Soffer EE, Chow EJ, Kong Y, Lin HC. Lower frequency of MMC is found in IBS subjects with abnormal lactulose breath test, suggesting bacterial overgrowth. *Dig Dis Sci.* Dec 2002;47(12):2639-2643.

14. Pimentel M, Mayer AG, Park S, Chow EJ, Hasan A, Kong Y. Methane production during lactulose breath test is associated with gastrointestinal disease presentation. *Dig Dis Sci.* Jan 2003;48(1):86-92.

15. Weinstock LB, Todorczuk JR, Fern SE, Thyssen EP. Comprehensive small intestinal bacterial overgrowth(SIBO) therapy for irritable bowel syndrome (IBS). *Am J Gastroenterol.* 2006;101(Suppl 2):S470-S471.

16. Walters B, Vanner SJ. Detection of bacterial overgrowth in IBS using the lactulose H2 breath test: comparison with 14C-D-xylose and healthy controls. *Am J Gastroenterol.* Jul 2005;100(7):1566-1570.

17. Khoshini R, Dai SC, Lezcano S, Pimentel M. A Systematic Review of Diagnostic Tests for Small Intestinal Bacterial Overgrowth. *Dig Dis Sci.* 2007; epub ahead of print.

18. Dinan TG, Quigley EM, Ahmed SM, et al. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? *Gastroenterology.* Feb 2006;130(2):304-311.

19. Barbara G. Mucosal barrier defects in irritable bowel syndrome. Who left the door open? *Am J Gastroenterol.* Jun 2006;101(6):1295-1298.

20. Barbara G, Stanghellini V, De Giorgio R, Corinaldesi R. Functional gastrointestinal disorders and mast cells: implications for therapy. *Neurogastroenterol Motil.* Jan 2006;18(1):6-17.

21. Yazar A, Buyukafpar K, Polat G, et al. The urinary 5-hydroxyindole acetic acid and plasma nitric oxide levels in irritable bowel syndrome: a preliminary study. *Scott Med J.* Feb 2005;50(1):27-29.

22. Hadley SK, Gaarder SM. Treatment of irritable bowel syndrome. *Am Fam Physician.* Dec 15 2005;72(12):2501-2506.

23. Wald A. Irritable bowel syndrome. *Curr Treat Options Gastroenterol.* Feb 1999;2(1):13-19.

24. Page JG, Dirnberger GM. Treatment of the irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). *J Clin Gastroenterol.* Jun 1981;3(2):153-156.

25. Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. *Aliment Pharmacol Ther.* Jan 1 2006;23(1):191-196.

26. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* Jul 18 2000;133(2):136-147.

27. Bardhan KD, Bodemar G, Geldof H, et al. A double-blind, randomized, placebo-controlled dose-ranging study to evaluate the efficacy of alosetron in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther.* Jan 2000;14(1):23-34.

28. Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. *Lancet.* Mar 25 2000;355(9209):1035-1040.

29. 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.* Jul 23 2001;161(14):1733-1740.

30. Chang L, Ameen VZ, Dukes GE, McSorley DJ, Carter EG, Mayer EA. A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. *Am J Gastroenterol.* Jan 2005;100(1):115-123.

31. Krause R, Ameen V, Gordon SH, et al. A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 mg and 1 mg alosetron in women with severe diarrhea-predominant IBS. *Am J Gastroenterol.* Aug 2007;102(8):1709-1719.

32. LOTRONEX (alosetron hydrochloride) [prescribing information]. Research Triangle Park, NC, 27709: GlaxoSmithKline; 2006.

33. Center for Drug Evaluation and Research. *FDA Public Health Advisory: tegaserod maleate (marketed as Zelnorm).* March 30, 2007 2007.

34. Videlock EJ, Chang L. Irritable bowel syndrome: current approach to symptoms, evaluation, and treatment. *Gastroenterol Clin North Am.* Sep 2007;36(3):665-685.

35. Clouse RE. Antidepressants for irritable bowel syndrome. *Gut.* Apr 2003;52(4):598-599.
36. Talley NJ, Kellow JE, Boyce P, Tennant C, Huskic S, Jones M. Antidepressant therapy (imipramine and citalopram) for irritable bowel syndrome: a double-blind, randomized, placebo-controlled trial. *Dig Dis Sci.* Jan 2008;53(1):108-115.
37. Yang J, Lee HR, Low K, Chatterjee S, Pimentel M. Rifaximin versus other antibiotics in the primary treatment and retreatment of bacterial overgrowth in IBS. *Dig Dis Sci.* Jan 2008;53(1):169-174.
38. 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.* Aug 2006;51(8):1297-1301.
39. Su C, Aberra F, Lichtenstein G. Utility of the nonabsorbed (<0.4%) antibiotic rifaximin in gastroenterology and hepatology. *Gastroenterol Hepatol.* 2006;2(3):186-197.
40. Di Stefano M, Malservisi S, Veneto G, Ferrieri A, Corazza GR. Rifaximin versus chlortetracycline in the short-term treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther.* May 2000;14(5):551-556.
41. Lauritano EC, Gabrielli M, Lupascu A, et al. Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther.* Jul 1 2005;22(1):31-35.
42. Cuoco L, Salvagnini M. Small intestine bacterial overgrowth in irritable bowel syndrome: a retrospective study with rifaximin. *Minerva Gastroenterol Dietol.* Mar 2006;52(1):89-95.
43. Esposito I, de Leone A, Di Gregorio G, et al. Breath test for differential diagnosis between small intestinal bacterial overgrowth and irritable bowel disease: An observation on non-absorbable antibiotics. *World J Gastroenterol.* Dec 7 2007;13(45):6016-6021.
44. Majewski M, McCallum R. 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.
45. Scarpellini E, Gabrielli M, Lauritano CE, et al. High dosage rifaximin for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther.* Apr 1 2007;25(7):781-786.
46. Frissora CL, Cash BD. Review article: the role of antibiotics vs. conventional pharmacotherapy in treating symptoms of irritable bowel syndrome. *Aliment Pharmacol Ther.* Jun 1 2007;25(11):1271-1281.
47. Pimentel M, Park S, Mirocha J, Kane SV, Kong Y. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of irritable bowel syndrome. *Ann Intern Med.* 2006;145(8):557-563.
48. 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.* Feb 2006;101(2):326-333.
49. Descombe JJ, Dubourg D, Picard M, Palazzini E. Pharmacokinetic study of rifaximin after oral administration in healthy volunteers. *Int J Clin Pharmacol Res.* 1994;14(2):51-56.
50. Trapnell C, Connolly M, Pentikis H, Forbes B. The absence of effect of oral rifaximin administration on the pharmacokinetics of ethinyl estradiol and

norgestimate contraceptive combination in healthy female volunteers. *Ann Pharmacother.*in press.
51. Trapnell CB, Connolly M, Pentikis H, Forbes WP, Bettenhausen DK. Absence of effect of oral rifaximin on the pharmacokinetics of ethinyl estradiol/norgestimate in healthy females. *Ann Pharmacother.* Feb 2007;41(2):222-228.
52. Quigley EM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. *Gastroenterology.* Feb 2006;130(2 Suppl 1):S78-90.
53. Kim HJ, Camilleri M, McKinzie S, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther.* Apr 1 2003;17(7):895-904.
54. Kajander K, Hatakka K, Poussa T, Farkkila M, Korpela R. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. *Aliment Pharmacol Ther.* Sep 1 2005;22(5):387-394.
55. Kajander K, Myllyluoma E, Rajilić-Stojanović M, et al. Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. *Aliment Pharmacol Ther.* Jan 1 2008;27(1):48-57.
56. 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.* Jul 2006;101(7):1581-1590.
57. Guyonnet D, Chassany O, Ducrotte P, et al. Effect of a fermented milk containing *Bifidobacterium animalis* DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. *Aliment Pharmacol Ther.* Aug 1 2007;26(3):475-486.

TABLE 1. Principal Symptom-Based Diagnostic Criteria for IBS

Manning criteria[9]

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

Rome III criteria[1]

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

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

IBS, irritable bowel syndrome.

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

Drug	Therapeutic class	Status
Lubiprostone	Chloride channel modulator	Approved 2008 (IBS-C)
Duloxetine	Serotonin norepinephrine reuptake inhibitor	Phase 4
Rifaximin	Nonsystemic antibiotic	Phase 3
Trimebutine	Opioid	Phase 3
Renzapride	Serotonin receptor antagonist	Phase 3 (IBS-C)
Clonidine	α_2-Adrenergic receptor agonist	Phase 2/3 (IBS-D)
Dextofisopam	GABA receptor agonist	Phase 2/3
Fedotozine	Opioid	Phase 2
Asimadoline	Opioid	Phase 2
Linaclotide acetate	Guanylate cyclase-C receptor agonist	Phase 2 (IBS-C)
Solabegron	β_3-adrenergic receptor agonist	Phase 1
Octreotide	Somatostatin analogue	Phase 1

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