Annals of Internal Medicine | ARTICLE

The Effect of a Nonabsorbed Oral Antibiotic (Rifaximin) on the Symptoms of the Irritable Bowel Syndrome

A Randomized Trial

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Background: Alterations in gut flora may be important in the pathophysiology of the irritable bowel syndrome (IBS).

Objective: To determine whether the nonabsorbed antibiotic rifaximin is more effective than placebo in reducing symptoms in adults with IBS.

Design: Double-blind, randomized, placebo-controlled study.

Setting: 2 tertiary care medical centers.

Participants: 87 patients who met Rome I criteria for IBS and were enrolled from December 2003 to March 2005.

Interventions: Participants who met enrollment criteria were randomly assigned to receive 400 mg of rifaximin 3 times daily for 10 days ($n = 43$) or placebo ($n = 44$). Eighty participants completed rifaximin therapy or placebo, and follow-up data were available for at least 34 participants per study group at any time point thereafter.

Measurements: A questionnaire was administered before treatment and 7 days after treatment. The primary outcome was global improvement in IBS. Patients were then asked to keep a weekly symptom diary for 10 weeks.

Results: Over the 10 weeks of follow-up, rifaximin resulted in greater improvement in IBS symptoms ($P = 0.020$). In addition, rifaximin recipients had a lower bloating score after treatment.

Limitations: The major limitations of the study were its modest sample size and short duration and that most patients were from 1 center.

Conclusions: Rifaximin improves IBS symptoms for up to 10 weeks after the discontinuation of therapy.

Ann Intern Med. 2006;145:557-563. www.annals.org
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ClinicalTrials.gov Identifier: NCT00259155.

The irritable bowel syndrome (IBS) is one of the most common chronic medical conditions (1–6), yet its cause is unknown. Among other contributors, alterations in gut flora have been identified as potentially important. Results of recent studies indicate that up to 84% of patients with IBS have an abnormal lactulose breath test result, suggesting small-intestinal bacterial overgrowth (7, 8). On the basis of this concept, the antibiotic neomycin can statistically significantly improve the symptoms of IBS (7, 8). In addition, the effect of neomycin correlates with the elimination of bacterial overgrowth, as indicated by the normalization of the lactulose breath test result (7, 8).

Although neomycin seems to improve symptoms, it effectively eliminates bacterial overgrowth in only about 25% of patients with IBS (8). Furthermore, side effects limit the use of neomycin. Low efficacy also applies to other antibiotics (for example, doxycycline and amoxicillin–clavulanate) that have been previously investigated for treating bacterial overgrowth (9). An ideal antibiotic for IBS is, arguably, one with negligible systemic absorption, minimal side effects, and high efficacy for bacterial overgrowth.

Rifaximin is a gut-selective antibiotic with negligible systemic absorption (≤0.4%) and broad-spectrum activity in vitro against gram-positive and gram-negative aerobes and anaerobes (10). On the basis of this broad spectrum, eradication rates with rifaximin in bacterial overgrowth are as high as 70% (11). Furthermore, rifaximin has a similar tolerability profile to that of placebo and has known activity against *Clostridium difficile* (12). These properties make it a good candidate for treating a condition that is as common as IBS.

Our study aimed to determine whether the nonabsorbed antibiotic rifaximin is more effective than placebo in reducing symptoms in adults with IBS.

METHODS

Setting and Participants

Our study was conducted at the Cedars-Sinai Medical Center, Los Angeles, California, and the University of Chicago, Chicago, Illinois. We recruited patients with IBS through advertising in local media (radio and news publications). We did not recruit patients from the IBS clinics of the Cedars-Sinai Gastrointestinal Motility Program to avoid enrollment of tertiary care patients. The institutional review board of both centers approved the study, and all patients provided written informed consent.

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Context

Few trials have evaluated the effects of antibiotics on symptoms of the irritable bowel syndrome (IBS).

Contribution

In this double-blind trial, 87 patients with IBS were randomly assigned to either rifaximin (400 mg 3 times daily) or placebo for 10 days. Over a 10-week follow-up period, the rifaximin recipients reported global improvements in overall symptoms and less bloating more frequently than the placebo recipients. No major differences in abdominal pain, diarrhea, or constipation were observed between the groups.

Cautions

The duration of therapy and follow-up was short.

Implications

Rifaximin may improve some symptoms in some patients with IBS.

—The Editors

Patients between 18 and 65 years of age who met Rome I criteria (13) were eligible. Exclusion criteria were the presence of underlying conditions that are known to predispose to bacterial overgrowth, including diabetes; narcotic use; previous bowel resection; inflammatory bowel disease; cirrhosis; known bowel adhesions; or any known chronic gastroenterological disease, such as celiac disease. We excluded patients who were taking tegaserod and antidepressants unless these treatments were discontinued before study entry. We also excluded participants who reported taking an oral antibiotic within the previous 3 months. After participant inclusion and exclusion, we recruited 84 participants from the Cedars-Sinai Medical Center and 3 participants from the University of Chicago. We followed participants in special research clinics at both centers.

Randomization and Interventions

Eligible patients completed a 7-day stool diary that was based on the Bristol stool form scale (14). Patients returned to the clinic after a 12-hour fast and completed a symptom questionnaire about the preceding 7 days of symptoms. We then randomly assigned patients to double-blind treatment with 400 mg of rifaximin 3 times daily for 10 days or a matching placebo. We chose this dosage on the basis of a previous study that demonstrated the efficacy of rifaximin in bacterial overgrowth (11). The randomization of rifaximin versus placebo was conducted outside of Cedars-Sinai Medical Center in a 1:1 ratio into blocks of 4 patients. The allocation sequence was determined and coded at Salix Pharmaceuticals, Morrisville, North Carolina. Since this was an investigator-initiated study, the rifaximin and placebo were distributed to the Cedars-Sinai Medical Center, and nonstratified medicine and placebo were sent to the University of Chicago in groups of 4 as enrollment progressed. The medicine and placebo were prepackaged to conceal content at all times. Research personnel who were involved in product distribution were also blinded to package content.

Assessments and Follow-up

After completing the 10-day course of study medication, patients immediately began another stool diary for 7 days then returned to complete a follow-up questionnaire and to return their pill container for a pill count to determine adherence.

Patients then entered the follow-up phase, during which they completed a weekly self-administered symptom questionnaire at home that documented their symptoms for an additional 9 weeks (for a total of 10 weeks of post-treatment follow-up). During this time, we asked participants to fax their responses to the research office. When a fax was not received on the appropriate day, research assistants called patients to ensure adherence. During this phase of study, no physician interaction occurred. During the last week of follow-up, patients completed a daily stool diary. At the end of the follow-up period, patients returned to the clinic for a final visit, which included another symptom questionnaire.

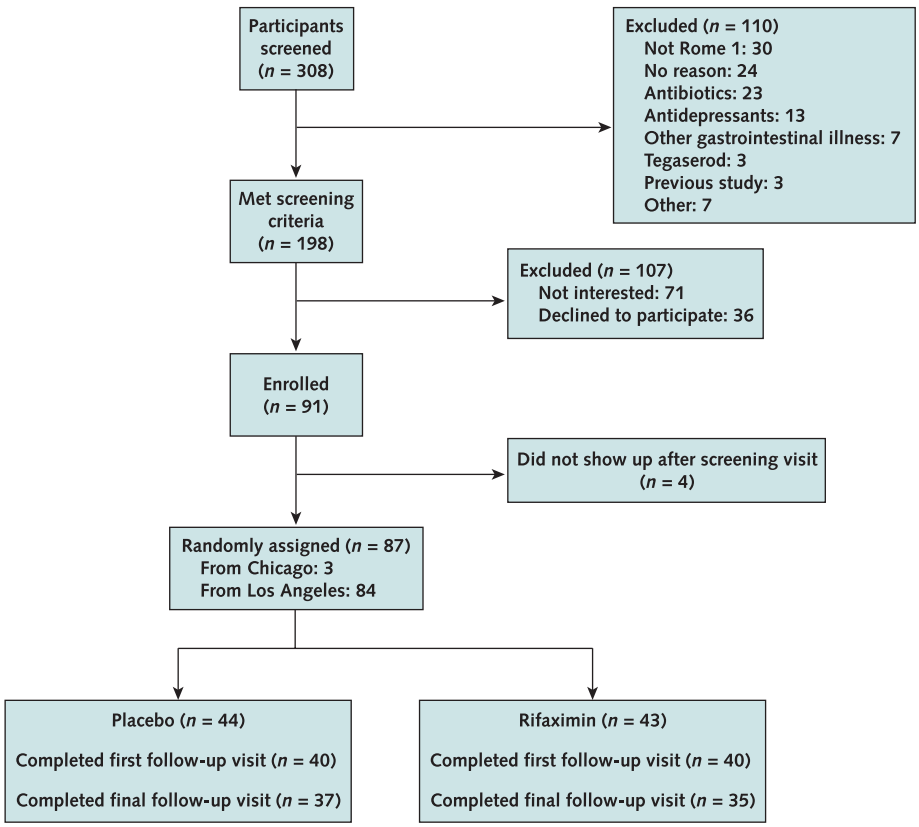
For the initial symptom questionnaire, patients were asked to indicate the severity of each of 9 symptoms (abdominal pain, diarrhea, constipation, bloating, urgency, incomplete evacuation, mucus, sense of incomplete evacuation, and gas) on a visual analogue scale (VAS) ranging from 0 mm to 100 mm, with 100 mm being extreme. We

Table 1. **Study Recruitment and Enrollment Summary**

Study Group	Patients Randomly Assigned to 10 Days of Rifaximin or Placebo, *n**	Patients Who Completed a Questionnaire during a Subsequent 10 Weeks of No Drug or Placebo, *n*†									
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9‡	Week 10
Total	87	82	74	76	74	73	72	71	70	68	72
Placebo	44	42	37	38	37	37	35	35	34	34	37
Rifaximin	43	40	37	38	37	36	37	36	36	34	35

* All patients completed a 7-day stool diary and questionnaire before randomization.
† Patients completed a 7-day stool diary before week 1.
‡ Patients completed a 7-day stool diary during this week.

Figure 1. **Study flow chart.**



used all 9 symptoms to verify IBS criteria in patients, but we assigned only diarrhea, constipation, abdominal pain, and bloating a priori as treatment end points. We asked patients to rate the severity of their symptoms on the VAS again 7 days after the completion of rifaximin treatment or placebo. Furthermore, we asked patients to provide a percentage of global improvement in their overall IBS symptoms from 0% to 100%. We chose global improvement since the Rome Consensus Group considers it to be the preferred end point measure in IBS treatment studies (15). Patients then rated the severity of their symptoms on the VAS and rated global improvement again each week for 8 weeks of follow-up and at the final visit to provide a total of 10 weeks of follow-up data. **Table 1** depicts the number of patients with outcomes at various time points during the study.

At the first follow-up visit, physicians evaluated adverse events by asking patients, in an open-ended manner, whether they had experienced adverse events while receiving therapy and to elaborate on any that occurred.

Although breath testing and breath methane level determinations were performed, we do not report them in our paper.

Statistical Analysis

We determined the number of patients for the study on the basis of the neomycin effect in a recent double-blind study for IBS on global improvement (8). To detect a difference of 35% (SD, 50%) with a power of 90%, we needed to assign 44 participants per group. Assuming a dropout rate of 10%, we calculated that approximately 96 patients would need to be recruited.

The primary end point was global improvement in IBS symptoms during follow-up. As seen in **Figure 1**, data were not available for all 10 weeks of follow-up.

We assessed the primary end point (percentage of global improvement) across the 10 weeks of follow-up by using an approach analogous to a repeated measures analysis of variance. Specifically, we used a mixed model with visit week (at 10 levels), treatment group (rifaximin or placebo), and group-by-week interaction as the fixed factors and patient as the random factor. The interaction and group factors were the main factors of interest in the analyses. We estimated mixed models by using the restricted maximum likelihood method.

Because the global improvement percentage varied widely across week for most individuals, we considered week to be a categorical variable in the mixed model.

Table 2. **Side Effects of Placebo and Rifaximin***

Side Effect	Placebo Recipients, *n*	Rifaximin Recipients, *n*
Abdominal pain	3	4
Constipation	2	1
Nausea	2	0
Vomiting	1	0
Bad taste	0	2
Fatigue	1	1
Straining	0	1
Urgency	0	1
Headache	1	0
Hemorrhoid	1	0
Rash	1	0
Gas	1	0
Fever	1	0

* Side effects were not statistically different between groups.

Within-patient correlation across time was addressed by an autoregressive (first-order) model for the covariance structure. Missing data were mostly intermittent, and we assumed them to be missing at random. The normality assumption was rarely satisfied in either group at any week. However, at least 34 observations were recorded per group per week and the sample sizes were well-balanced, so we used the mixed-model analysis. We analyzed models with a single covariate (baseline diarrhea, constipation, abdominal pain, or bloating severity score). The covariate models did not improve the fit nor did they change the substantive results. Hence, we presented the simpler (no covariate) model results.

We used a similar mixed-model approach to assess the secondary end points of abdominal pain, bloating, diarrhea, and constipation. Within-patient correlation was modeled by an autoregressive covariance structure. The normality assumption was rarely satisfied for the diarrhea outcome, with a similar floor effect for the primary outcome. The pain and constipation outcomes occasionally satisfied the normality assumption. The bloating outcome was usually compatible with a sample from a normal distribution. At least 34 observations were available in each group at each week, and good balance was achieved across groups. Since abdominal pain seemed higher in the rifaximin than in the placebo group (**Table 2**), we conducted further analysis using pain as a covariate. While baseline constipation was slightly lower in the rifaximin group, we observed no interaction when constipation was a covariate.

All values were expressed as means (SD). We set statistical significance at a P value less than 0.05. We determined statistical analysis by using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Role of Funding Source

The study was funded by a grant from Salix Pharmaceuticals. The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Demographic Characteristics

We screened 308 participants but excluded 110 of them for various reasons (**Figure 1**). The most common reasons for exclusion were not meeting the Rome I criteria, nonspecific reasons, and recent antibiotic and antidepressant use, which left 198 participants who met the screening criteria. Of these, 87 participants agreed to participate and were randomly assigned to rifaximin or placebo (**Figure 1**). Seven of the 87 patients (8%) prematurely withdrew (3 rifaximin recipients and 4 placebo recipients). The reasons for withdrawal were not returning for a follow-up visit ($n = 3$), receiving an antibiotic for other reasons ($n = 2$), and having side effects ($n = 2$). The side effects leading to premature withdrawal were pruritus ($n = 1$) and worsening diarrhea and nausea ($n = 1$), both of which occurred in the placebo group. **Figure 1** depicts the study design and number of patients with data at that time point for global improvement. In the rifaximin group, 1 patient developed an increase in diarrhea severity score that resolved spontaneously, allowing the patient to complete the study. Among the 87 patients in the intention-to-treat study sample, 44 received placebo and 43 received rifaximin. Among the 66 patients who returned their pill container after treatment, 85% of participants took at least 90% of pills. The demographic characteristics were similar for the 2 groups (**Table 3**), although average baseline abdominal pain was more severe and constipation was less severe in the rifaximin group.

Response to Rifaximin

We modeled the global improvement percentage as a function of group, week, and group-by-week interaction. The group main effect was significant ($P = 0.020$), and the group-by-week interaction and week effects were not significant ($P = 0.78$ and 0.96, respectively). **Figure 2** presents the profiles of global improvement percentages for the groups. The profiles were essentially parallel across week (no interaction effect) and the mean values in the rifaximin group were elevated compared with those in the placebo group (group main effect), indicating the superiority of rifaximin across the 10 weeks. Rifaximin recipients

Table 3. **Comparison of Demographic Characteristics and Baseline Symptom Scores in the Placebo and Rifaximin Study Groups***

Characteristic	Placebo Group ($n = 44$)	Rifaximin Group ($n = 43$)
Age, *y*	38.2 (9.8)	39.1 (12.5)
Weight, *kg*	157.6 (49.2)	160.9 (37.5)
Men/women, *n/n*	15/29	14/29
Abdominal pain severity score	36.8 (29.8)	52.4 (28.8)
Diarrhea severity score	35.3 (34.4)	42.6 (37.4)
Bloating severity score	54.5 (32.3)	54.0 (25.8)
Constipation severity score	48.0 (34.4)	35.7 (33.4)

* Data are expressed as mean (SD), unless otherwise noted.

experienced an average improvement of 36.40% (SD, 31.46%) compared with 21.00% (SD, 22.08%) for placebo recipients.

Secondary Symptoms and Rifaximin

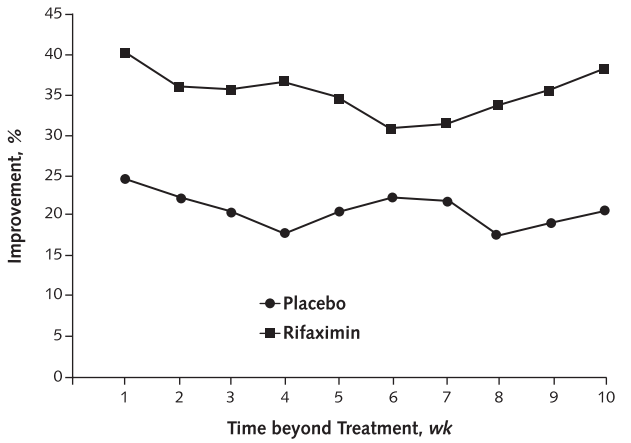
By using a model similar to that for evaluating global improvement, we assessed the individual bowel symptoms of abdominal pain, bloating, diarrhea, and constipation. On the basis of a model as a function of assigned group (rifaximin or placebo), the VAS scores were significantly better in the rifaximin group during the 10-week follow-up for bloating ($P = 0.010$). The VAS scores for abdominal pain ($P = 0.32$), diarrhea ($P = 0.67$), and constipation ($P = 0.069$) did not significantly differ.

However, since abdominal pain was greater in the rifaximin group at baseline, we studied abdominal pain as a covariate. Abdominal pain did not affect the global improvement outcome in a fixed-effects model. Baseline abdominal pain did statistically significantly interact with the diarrhea and bloating outcomes. After controlling for abdominal pain, our analysis found that bloating remained significantly improved ($P < 0.001$), although VAS scores for diarrhea were still not statistically significant over placebo ($P = 0.151$).

Tolerability of Rifaximin

Table 2 compares the side effects reported by patients during treatment. The most common side effects with rifaximin were abdominal pain, diarrhea, and a bad taste in the mouth. However, these occurred rarely and the incidence was similar between the groups.

Figure 2. **Overall improvement of the irritable bowel syndrome with rifaximin during 10 weeks of follow-up on the basis of a mixed multivariate model.**



Mean improvements after 10 weeks: 36.40% (SD, 31.46%) for rifaximin and 21.00% (SD, 22.08%) for placebo ($P = 0.020$). The P value represents the treatment group effect for the 10-week period on the outcome of the percentage of global improvement. The group-by-week interaction and week effects were not statistically significant; therefore, being in the rifaximin group was the main factor associated with the improvement.

DISCUSSION

The cause of IBS remains elusive, but evidence suggests an important role of enteric bacteria and a potential role of antibiotics in its treatment (7, 8). In our randomized, double-blind, placebo-controlled study, the nonabsorbable broad-spectrum antibiotic rifaximin statistically significantly improved global IBS symptoms compared with placebo. These improvements with rifaximin over placebo were seemingly maintained through most of the 10-week follow-up.

Rifaximin is a newly approved, nonabsorbable broad-spectrum antibiotic derived from the rifamycin family. Its broad-spectrum coverage includes gram-positive, gram-negative, aerobic, anaerobic, and microaerophilic bacteria and has received initial U.S. Food and Drug Administration approval for treating travelers' diarrhea in the United States. Studies from Europe and the United States demonstrate that the spectrum of coverage and favorable safety profile have made rifaximin a potential treatment or adjunct treatment of many bacterially related gastrointestinal disorders, such as Crohn disease (16, 17), and for preventing travelers' diarrhea (18), hepatic encephalopathy (19), and *C. difficile*–associated diarrhea (12). In 2000, rifaximin was shown to have a 70% likelihood of normalizing a lactulose breath test result in patients with suspected small-intestinal bacterial overgrowth, which prompted its evaluation for IBS (11).

Enteric flora in patients with IBS differ from enteric flora in healthy people. Studies in which stool was cultured showed some degree of deficiency of lactobacilli and bifidobacteria (20). This finding has led to an increasing use of probiotics in IBS (21). Some benefit is seen with bifidobacteria but not with lactobacilli, and more work is needed in this area. However, the beneficial effects of replacing a single organism in the complex milieu of bacteria (400 species) in the colon are unknown.

Another recent association between gut bacteria and IBS relates to the finding of bacterial overgrowth. Up to 84% of patients with IBS have an abnormal lactulose breath test result, which suggests the presence of bacterial overgrowth (8). However, proof of bacterial overgrowth would require culture of the small bowel. Although culture is critical to identifying a bacterial source of symptoms in most cases, it is far from a gold standard for identifying small-intestinal bacterial overgrowth. Eighty percent of all normal gastrointestinal flora cannot be cultured because of unknown and usually fastidious nutrient requirements. In addition, the ideal location for culturing the small bowel is beyond the mid–small bowel, which is not easily accessible. A literature search of studies published before July 2006 provides some further evidence for the utility of antibiotics in IBS. In a recent study, neomycin treatment improved IBS in a manner dependent on the improvement of the lactulose breath test result (8). One concern in the study

was the short duration of follow-up. More important, the emergence of the new nonabsorbed antibiotic rifaximin is now showing great promise in clinically improving IBS in open-label (22), retrospective (23), and controlled studies (24). In our study, rifaximin was associated with similar clinical improvement with no notable side effects. Furthermore, benefits were sustained for 10 weeks after only 10 days of therapy.

The placebo response rate in our study deserves some discussion. Studies of IBS often report high placebo response rates, such as recent studies on the efficacy of serotonin receptor agonists and antagonists (25–28). However, these rates cannot reliably be compared with those of our study. In the serotonin studies, the placebo response is tracked for the 2 to 3 months of drug treatment. In our study, the premise and finding is that rifaximin is treating an underlying cause of IBS, whereby the drug is required only for a short time with benefits lasting for 10 weeks after treatment. Since both groups of patients (both rifaximin recipients and placebo recipients) understood that they were no longer taking any agent after 10 days, the placebo effect should have been minimal during follow-up.

Several considerations apply to the use of antibiotics for IBS. Potential widespread or prolonged use of antibiotics may contribute to bacterial resistance. The use of rifaximin for IBS may mitigate a potential contribution to bacterial resistance. Because rifaximin is gut-selective and less than 0.4% is absorbed, it has little or no therapeutic utility beyond enteric infections. In addition, our data suggest that long-term treatment, which may increase bacterial resistance, is not necessary for sustained clinical benefit with rifaximin. We believe our study is the first to demonstrate a sustained benefit of a pharmacotherapy for IBS after discontinuation of therapy. In this respect, rifaximin differs from tegaserod, with which symptoms return to baseline after therapy is stopped. These differing outcomes suggest that rifaximin addresses a causative factor in IBS.

Some limitations of our study deserve comment. First, while the study results demonstrate efficacy in a relatively small group of patients with IBS, side effects may be difficult to assess in such a small study when considering the potentially large patient population with IBS. Second, while a global measure of symptoms, diarrhea, and bloating seemingly improved with therapy, a larger study is necessary to specifically evaluate the effects of therapy on other symptoms, such as constipation. The study duration may also be an issue. Although our study is as long as most drug trials in IBS, symptoms may recur in such a trial if bacterial overgrowth is assumed to be the cause of IBS. The study duration was too short to recognize any meaningful recurrence. Furthermore, most patients were from 1 center, and although other centers are duplicating our results (22–24), a large-scale, multicenter study of rifaximin in IBS is needed.

In summary, the antibiotic rifaximin resulted in statistically greater global improvement in IBS than placebo in our randomized, double-blind study. Improvements were sustained through 10 weeks of follow-up despite cessation of therapy after only 10 days. Recent data suggest that the optimal dosage of rifaximin may, in fact, be higher than that used in our study (22). Finally, this new concept of IBS treatment will warrant future studies that allow for head-to-head comparison of antibiotics to other treatment strategies for IBS, such as prokinetics and probiotics.

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Acknowledgments: The authors thank Tess Constantino, RN, and Vicki Lees-Kim, RN, for their assistance with patient coordination; Robert Wade for his vast experience with lactulose breath testing; and Dr. Soumya Chatterjee for his assistance in auditing the data. In addition, they thank the Beatrice and Samuel A. Seaver Foundation, which has been a gracious supporter of the work on gut bacteria and IBS.

Grant Support: By Salix Pharmaceuticals.

Potential Financial Conflicts of Interest: *Consultancies:* M. Pimentel (Novartis, Chugai Pharmaceutical, Promethus, Romark, Salix Pharmaceuticals); *Honoraria:* M. Pimentel (Novartis, Salix Pharmaceuticals); *Grants received:* M. Pimentel (Salix Pharmaceuticals); *Patents received:* M. Pimentel (Cedars-Sinai Medical Center); *Patents pending:* M. Pimentel (Cedars-Sinai Medical Center). Cedars-Sinai Medical Center has a licensing agreement with Salix Pharmaceuticals.

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