

## Treatment for Bacterial Overgrowth in the Irritable Bowel Syndrome

Over the last 10 to 20 years, the irritable bowel syndrome (IBS) has garnered considerable scientific interest. The acceptance of the biopsychosocial model (1), the application of symptom-based diagnostic criteria (for example, Rome diagnostic criteria), and the growth in biological and behavioral measurement technology (2, 3) has created a fertile area for new research in IBS with the potential for more effective treatments. Research now focuses on altered motility and neuroenteric signaling; visceral hypersensitivity and its enhancement by inflammation and altered mucosal immunity; and brain–gut dysfunction via altered pain, autonomic, and stress-related (for example, corticotropin-releasing hormone) pathways (2, 3). It is now evident that IBS is not a single disease but is a well-characterized symptom complex that relates symptoms to a variety of underlying physiologic determinants from gut to brain and back. Thus, a single “magic bullet” for the disorder is unlikely: Treatments will be used alone or in combination to target the altered physiologic determinants that are unique to each individual.

The role of the bacterial flora, a new area of research in the clinical expression of IBS, has developed from several lines of evidence: the recognition of postinfectious IBS in susceptible hosts after bacterial gastroenteritis (4, 5); the finding of an altered colonic bacterial ecology as manifested by stool cultures in patients with IBS compared with controls (6); the potential benefit of treating IBS with probiotics, presumably to replace “bad” bacteria with “good” bacteria (for example, bifidobacteria [7, 8] and lactobacilli [8]) and reduce mucosal inflammation (9); and the evidence for small-bowel bacterial overgrowth in some patients with IBS (10–13). With regard to the latter, a research group has identified, by using lactulose H<sub>2</sub> breath assessment, high frequencies of bacterial overgrowth in IBS over the last several years: About 84% of patients with IBS, compared with 20% of healthy controls, had abnormal lactulose H<sub>2</sub> breath study results. This research group has also shown that patients with IBS who were treated with neomycin may normalize their lactulose H<sub>2</sub> breath test result (40% of neomycin recipients vs. 15% of placebo recipients) and may gain a modest clinical improvement (35% of neomycin recipients vs. 11% of placebo recipients;  $P < 0.05$ ) (11, 12).

In this issue, Pimentel and colleagues (14) extend their previous work by evaluating the efficacy of a newer broad-spectrum nonabsorbable antibiotic, rifaximin (1200 mg/d for 10 days), which is thought to produce a better clinical response on symptoms than traditional antibacterial agents (15), and by measuring clinical response for up to 10 weeks after treatment. The study found that, when averaged over the 10-week period, the mean percentage of global improvement was significantly better for rifaximin (36.4% [SD, 31.5%]) than for placebo (21.0% [SD, 22.1%]) ( $P =$

0.020). In the secondary analysis, only bloating improved, and abdominal pain, diarrhea, and constipation did not improve. Side effects reported in open interviews were minimal. The authors concluded that rifaximin treatment for 10 days showed greater global improvement than placebo, and the effects were sustained for 10 weeks.

Demonstrating benefit from a short course of an antibiotic for a sustained period of time in unselected patients with IBS is certainly novel and important. However, several methodologic issues must be addressed before drawing such conclusions from the study.

First, site recruitment differed markedly between the 2 study sites (83 participants vs. 3 participants). This raises questions about differences in the eligibility or recruitment strategy between sites, given that presumably the same recruitment protocols were used.

Second, the primary outcome measure was the percentage of improvement in IBS global scores of all patients in each treatment group averaged over the 10-week period. This end point is unique in the spectrum of IBS trials in the last decade and makes comparisons with other trials difficult. The end point is expressed as mean proportions (with SDs) of improvement across groups. Responders are not clearly defined a priori in Pimentel and colleagues' analysis, and hence the clinical significance of the proportion of response is unclear. The more traditional approach would be to define a responder on the basis of a binary adequate relief measure or satisfactory relief (16, 17). Moreover, most clinical trials provide statistical data on treatment differences between groups by week. Whether the averaged 36.4% response rate is clinically meaningful relative to the placebo response rate of 21.0% is unclear.

Third, since the global measure includes pain, the imbalance in baseline pain scores is important to note. The imbalance (higher baseline pain scores in the rifaximin group) favors the reduction in the global measure with rifaximin.

Fourth, none of the secondary end points, which are integral in defining IBS (namely pain, diarrhea, and constipation), improved with treatment, suggesting that rifaximin may be targeted more for bloating (18).

Fifth, Pimentel and colleagues' primary analysis (mixed models) is not conventional for a primary determination of effectiveness. It allows restructuring of the data set to use several observations for each patient. Usually one evaluates the effectiveness of an intervention at a given prespecified time point. Furthermore, this approach minimizes the effect of dropouts and differs from a typical intention-to-treat analysis, where the values for the dropouts are usually imputed with a best worst-case scenario, thus providing limits to the effectiveness of the intervention. Thus, how the results would have fared in a more standard

intention-to-treat analysis with a defined end point and adjustments for dropouts is unclear.

Finally, although lactulose breath test studies were done before and after treatment, data relating to the prevalence of the abnormal test results in each group and the correlation of clinical response to reduction in test scores were not reported. These data, if completed, might provide some mechanistic evidence for effects, and such data were presented in Pimentel and colleagues' previous trial (11).

Thus, while one could conclude from the study that rifaximin could be beneficial for treating bloating and global symptoms in IBS, the limitations of the study make the findings inconclusive and raise questions about the clinical significance of the results.

The premise that antibiotics are useful for treating IBS is based on certain assumptions that must be addressed before clinical recommendations can be made. The first assumption, arising primarily from the authors' research group (10–12), is that the vast majority of patients with IBS (about 80%) have bacterial overgrowth as measured by the lactulose H<sub>2</sub> breath test. This has generated controversy because other groups do not confirm the same prevalence and often quote a more conservative figure of about 10% (19, 20).

The second assumption is that the lactulose breath test accurately detects bacterial overgrowth. One study (21) showed only 17% sensitivity when compared with jejunal culture. Another study (22) reported that the test has low specificity (44%) because the abnormal breath test result may reflect rapid small-bowel transit. This is an important issue, especially in patients with abnormally fast small-bowel transit that leads to metabolism of the lactulose by cecal bacteria. This is also more likely to occur when the sensitivity of the study is enhanced by carrying out the measurement to 180 minutes. Thus, the lactulose test is a surrogate measure, rather than a diagnostic standard, for bacterial overgrowth or rapid intestinal transit.

A third assumption is that antibiotics can lead to symptomatic benefit when bacterial overgrowth is present. Although this assumption is supported by several studies, at least 1 study (23) has shown that prescribing antibiotics in general for nongastrointestinal reasons leads to an increase in functional gastrointestinal symptoms.

Finally, one must consider the mechanistic evidence for an association between symptomatic response to antibiotics and a reduction of abnormal lactulose H<sub>2</sub> breath study scores. In a previous study (11), the findings were statistically significant but the association was modest.

In the end, we must consider how the practitioner should apply this information in clinical practice. Should lactulose breath testing be done first and should treatment be started if the result is positive ("test and treat"), or should antibiotics be routinely prescribed? Several will still doubt the evidence for the described associations. The prevalence of bacterial overgrowth in IBS seems lower than that proposed, and bacterial overgrowth is difficult to di-

agnose because the lactulose breath test is relatively insensitive and nonspecific, while duodenal aspiration is cumbersome and even its accuracy has been questioned (14). Finally, the benefit of using antibiotics is not fully proven and must be balanced with potential risks in terms of side effects, high costs (a 10-day course of rifaximin is \$250, and a breath test, if ordered, costs an additional \$304), and the need for recurrent treatments. Furthermore, in clinical practice, a therapeutic trial is difficult because patients have high expectations for benefit when antibiotics are prescribed, which can produce a placebo response. When the symptoms recur, the clinical decision-making cycle must be repeated.

The clinical challenge is to identify the subset of patients with IBS who are most likely to have bacterial overgrowth that produces symptoms relative to the many other factors (such as abnormal motility, visceral hypersensitivity, and psychosocial distress factors) contributing to patients' clinical state. Unfortunately, no data are available to help us in this decision, so I suggest the following on the basis of personal experience and limited data. First, determine whether the patient fits the clinical profile of bacterial overgrowth with postprandial abdominal discomfort, bloating, and possibly loose stools. If the clinical features are present, perform a lactulose H<sub>2</sub> breath study if it is available and, if the result is positive, consider a course of a broad-spectrum antibiotic. After this, treat the patient with a probiotic to provide more "good" bacteria and, if the stool normalizes or becomes more constipated, consider adding a prokinetic agent to increase small-bowel transit. If symptoms recur and the previous lactulose test result was positive, repeat the study and retreat with antibiotics only if the lactulose H<sub>2</sub> breath test result is again positive. If lactulose testing is not available, the clinician should be conservative and should not repeat treatments unless a clear and sustained benefit is evident for at least several months.

Pimentel and colleagues should be congratulated for their efforts to increase awareness of this important subgroup of patients with IBS symptoms who need to be identified and treated. However, until better evidence is available, decisions relating to diagnosis and treatment remain within the art of medicine.

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