Bacteria and the Role of Antibiotics in Irritable Bowel Syndrome

by Mark Pimentel

Although several pathophysiologic models have been suggested, the etiology of irritable bowel syndrome (IBS) is unknown. Emerging evidence suggests that small intestinal bacterial overgrowth (SIBO) may explain some symptoms associated with IBS. The putative contribution of bacteria to IBS pathophysiology and symptoms provides a rationale for investigating the efficacy and safety of antibiotics in IBS. Although few controlled studies have been conducted, evidence has suggested that antibiotics may reduce the presence of SIBO and improve symptoms of IBS. Several antibiotics, including rifaximin and neomycin, have been shown to effectively reduce bacterial overgrowth and improve bowel symptoms in patients with SIBO and/or IBS. Rifaximin may be well suited for the treatment of IBS due to its favorable safety profile. Further research is warranted to more fully elucidate the role of bacteria in IBS and the therapeutic benefits of antibiotics in the treatment of IBS.

KEY WORDS: small intestinal bacterial overgrowth, rifaximin, neomycin

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by symptoms, such as abdominal pain, bloating, diarrhea, and constipation, that are not attributable to structural or biochemical abnormalities (1). Although several conceptual models of IBS pathogenesis have been suggested, including visceral hypersensitivity, abnormal intestinal motility, immune activation, and altered brain-gut interactions, none fully explain the heterogeneous range of symptoms associated with IBS (1,2). Emerging evidence suggests that bacteria, specifically small intestinal bacterial overgrowth (SIBO), may be involved in producing some IBS symptoms (3,4). These findings provide a rationale for the potential therapeutic benefit of antibiotic therapy. This article

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reviews clinical data suggesting the involvement of bacteria in IBS as well as data available for the efficacy and safety of antibiotics in treating SIBO and IBS.

**EVIDENCE FOR BACTERIAL INVOLVEMENT IN IBS**

Small intestinal bacterial overgrowth involves abnormal colonization and growth in the small intestine of endogenous bacteria resembling those normally found in the colon (5–8). A potential link between SIBO and IBS has been suggested not only by similarities in symptoms (e.g., diarrhea, abdominal discomfort, bloating, and flatulence) (6,8,9) but also by the reported prevalence of SIBO in patients with IBS (10–16). In studies using lactulose or glucose breath testing, SIBO was detected in up to 84% of patients who met Rome I (10,11) or Rome II (12–16) criteria for IBS (Table 1). Because breath tests indirectly measure bacteria and are associated with relatively low sensitivity and specificity (8), many authors believe direct bacterial assessment of intestinal aspirate cultures provides a better method for detecting SIBO (3–5) despite technical limitations, including lack of accessibility to the distal small intestine and potential for contamination during sampling (4). In direct sampling studies using jejunal aspirates, SIBO was observed in 4%–12% of patients with IBS (Table 1) (17,18), with similar results reported for healthy volunteers (18). However, because bacterial levels >5 x 10^3 colony-forming units (CFU)/mL were observed in the cultures of a significantly higher percentage of patients with IBS (43%) compared with healthy volunteers (12%; p = 0.002) (18), the standard definition of SIBO in culture studies (>10^5 CFU/mL [8]) may not accurately reflect bacterial overgrowth in patients with IBS. Although controversies and discrepancies exist with regard to the most accurate method for detecting and defining SIBO (6,8), these findings suggest that intestinal bacteria may play a role in producing bowel symptoms in a subset of patients. Furthermore, although few controlled clinical studies have been published, reports that antibiotic therapy normalized breath test results (10–13,19–21) and improved IBS symptoms (10,11,20,22,23) provide support for the potential role of bacteria in IBS in some patients.

**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactulose breath test</strong></td>
<td></td>
<td></td>
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<tr>
<td>Nucera, et al (13)</td>
<td>200</td>
<td>75</td>
</tr>
<tr>
<td>Nucera, et al (12)</td>
<td>98</td>
<td>65</td>
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<tr>
<td>Pimentel, et al (11)</td>
<td>202</td>
<td>78</td>
</tr>
<tr>
<td>Pimentel, et al (10)</td>
<td>111</td>
<td>84</td>
</tr>
<tr>
<td>Walters, et al (14)</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td><strong>Glucose breath test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCallum, et al (16)</td>
<td>143</td>
<td>38</td>
</tr>
<tr>
<td>Lupascu, et al (15)</td>
<td>65</td>
<td>31</td>
</tr>
<tr>
<td><strong>Jejunal aspirate cultures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simrén, et al (17)</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Posserud, et al (18)</td>
<td>162</td>
<td>4</td>
</tr>
</tbody>
</table>

IBS = irritable bowel syndrome; SIBO = small intestinal bacterial overgrowth.

**ROLE OF SIBO IN PRODUCING IBS SYMPTOMS**

**Bloating and Excess Gas Production**

Gas-related symptoms (e.g., bloating, abdominal pain and distention, and/or increased flatulence) have been reported in the majority (82%–92%) of patients with IBS (24,25) and did not appear to be dependent on the predominant IBS symptom (i.e., constipation, diarrhea, or alternating) (26). Bacterial gas production may provide a possible explanation for abdominal bloating and distention associated with IBS. Intestinal hydrogen gas, the production of which takes place primarily in the terminal ileum and colon, is a normal product of bacterial fermentation of food not easily digested and absorbed in the proximal small intestine (3). When SIBO is present, abnormal concentrations of colonic bacteria in the proximal small intestine allow for fermentation of easily and poorly digested food, thereby increasing gas production in this region (3).
The presence of excess intestinal gas in patients with IBS is supported by two radiographic studies of 37 and 60 patients, respectively, that showed significantly higher levels of abdominal gas in patients with IBS compared with healthy participants (p < 0.01 and p < 0.001, respectively) (24,27). Increased levels of gas were observed in patients with IBS regardless of the predominant bowel symptom (27).

Patients with IBS frequently report worsening of symptoms, such as excess gas and abdominal pain, following food ingestion (3,28). Foods high in carbohydrates and starch, which provide good substrates for bacterial fermentation, may be especially likely to cause these symptoms (28). However, most patients with IBS are usually unable to identify specific food triggers, suggesting that increases in the concentration of proximal intestinal bacteria, rather than a specific food type, may be responsible for postprandial bloating in IBS (3,28). In an investigation of postprandial gas production, gas excretion and production following consumption of a standardized meal were 2 and 4 times higher, respectively, in six patients with IBS compared with six healthy participants (p < 0.05) (29). Because no evidence of malabsorption was observed, the authors attributed increased gas production to alterations in the fermentation process (29).

Data suggest that gas-related IBS symptoms, such as bloating, may originate in the small intestine. In two studies of 22 and 40 patients, respectively, in which gas was infused into the jejunum, patients with IBS or bloating exhibited significant impairment of gas transit and clearance compared with healthy participants (p < 0.05 and p < 0.01 for each study, respectively) (30,31). In contrast, no impairment of colonic transit was observed following gas infusion (30). Several investigators have suggested that gas-handling alterations may be due to reduced intestinal motility (2,4), which, as discussed later, may be affected by bacterial gas production.

**Constipation.** Methane in the distal gut has been shown to slow intestinal transit and has been associated with reduced plasma levels of serotonin, a neurotransmitter that stimulates peristalsis (32,33). The role of methane in constipation was suggested by a study of 39 patients with constipation-predominant IBS that showed antibiotic treatment resulted in greater improvement in overall IBS symptoms for patients who produced high levels of methane compared with those who produced only high levels of hydrogen (p < 0.05) (34). Findings from two other breath test studies suggested that constipation in patients with IBS may be related to the type of gas produced by intestinal bacteria (10,35). High methane excretion was associated with constipation-predominant IBS but not diarrhea-predominant IBS. All 18 patients in the two studies combined who excreted high levels of methane alone were diagnosed with constipation-predominant IBS. In contrast, none of the 145 total patients with diarrhea-predominant IBS excreted high levels of methane alone (10,35). Patients who excreted high levels of methane also reported greater constipation severity compared with patients who did not excrete high levels of methane (p < 0.01) (10). However, other researchers observed no correlation between methane excretion and predominant bowel symptoms or symptom severity in 78 patients with IBS (36), suggesting that additional research is needed to determine the role of methane in IBS.

**ANTIBIOTIC TREATMENT OF SIBO AND IBS**

**Rifaximin**

Rifaximin is an oral, broad-spectrum antibiotic with localized action in the GI tract and low (<0.4%) systemic absorption (37). First marketed in Italy in 1987, rifaximin has been approved in 21 countries for a variety of indications (37–39). Although rifaximin is currently approved in the United States only for the treatment of travelers’ diarrhea (39), data suggest it may be effective in the treatment of SIBO (19–22,40–44) and IBS (22,23,44). In prospective and retrospective studies, rifaximin 600–1,600 mg/day for 5–14 days reduced hydrogen excretion compared with pretreatment levels (20–22) and normalized breath test results in 17%–80% of patients (Table 2) (19,20,41–44), with higher doses producing higher normalization rates. Rifaximin 800–1,200 mg/day for 5–14 days has also been shown to improve symptoms associated with SIBO (20,40,43,44). In a placebo-controlled study of 124 patients with gas-related symptoms who received rifaximin 800 mg/day for 10 days, a reduction in...
### Table 2
**Studies of Rifaximin for the Treatment of SIBO and/or IBS**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study type</th>
<th>Diagnosis</th>
<th>N</th>
<th>Treatment</th>
<th>Breath test normalization (%)</th>
<th>Symptom improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauritano et al (19)</td>
<td>Prospective, randomized</td>
<td>SIBO*</td>
<td>90</td>
<td>Rifaximin 600, 800, or 1,200 mg/day for 7 days</td>
<td>17, 27, 60**</td>
<td>NR</td>
</tr>
<tr>
<td>DiStefano et al (20)</td>
<td>Prospective, randomized, double-blind</td>
<td>SIBO***</td>
<td>21</td>
<td>Rifaximin 1,200 mg/day or chlortetracycline 1 g/day for 7 days</td>
<td>70 (R) vs 27 (C)**</td>
<td>Rifaximin reduced cumulative and diarrhea symptom scores vs baseline</td>
</tr>
<tr>
<td>Corazza et al (43)</td>
<td>Prospective, open-label</td>
<td>SIBO******</td>
<td>12</td>
<td>Rifaximin 800 or 1,200 mg/day for 5 days</td>
<td>67, 67</td>
<td>Symptom improvement observed in 83% of patients</td>
</tr>
<tr>
<td>Baidoo et al (40)</td>
<td>Prospective, open-label</td>
<td>SIBO******</td>
<td>14</td>
<td>Rifaximin 800 mg/day for 14 days</td>
<td>NR</td>
<td>Symptom improvement observed in 93% of patients; 86% achieved complete remission</td>
</tr>
<tr>
<td>Scarpellini et al (41)</td>
<td>Prospective, randomized</td>
<td>SIBO* and IBS</td>
<td>80</td>
<td>1,200 or 1,600 mg/day for 7 days</td>
<td>58, 80</td>
<td>NR</td>
</tr>
<tr>
<td>Gabrielli et al (42)</td>
<td>Prospective, randomized</td>
<td>SIBO*</td>
<td>120</td>
<td>Rifaximin 1,200 mg/day or metronidazole 750 mg/day or levofloxacin 500 mg/day for 7 days</td>
<td>62 (R) vs 45 (M) vs 60 (L)</td>
<td>NR</td>
</tr>
<tr>
<td>DiStefano et al (21)</td>
<td>Prospective, randomized, double-blind</td>
<td>Functional bowel disorders</td>
<td>34</td>
<td>Rifaximin 800 mg/day or activated charcoal 800 mg/day for 7 days</td>
<td>NR</td>
<td>Rifaximin reduced overall symptom severity vs baseline******</td>
</tr>
<tr>
<td>Sharara et al (22)</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>Gas-related bowel symptoms</td>
<td>63</td>
<td>Rifaximin 800 mg/day or placebo for 10 days</td>
<td>NR</td>
<td>Improvement in overall symptom severity reported in 41% of patients in rifaximin group vs 23% with placebo******</td>
</tr>
<tr>
<td>Yang et al (44)</td>
<td>Retrospective, chart review</td>
<td>SIBO and IBS********</td>
<td>84</td>
<td>Rifaximin 1,200 mg/day for 10 days</td>
<td>56</td>
<td>Symptom improvement observed in 69% of patients</td>
</tr>
<tr>
<td>Pimentel et al (23)</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>IBS********</td>
<td>87</td>
<td>Rifaximin 1,200 mg/day or placebo for 10 days</td>
<td>NR</td>
<td>Greater global improvement with rifaximin************; sustained for 10 weeks posttreatment</td>
</tr>
</tbody>
</table>

C = chlortetracycline; IBS = irritable bowel syndrome; L = levofloxacin; M = metronidazole; NR = not reported; R = rifaximin; SIBO = small intestinal bacterial overgrowth. *Based on glucose breath test results; **p < 0.001 vs 600 mg/day and p < 0.01 vs 800 mg/day; assessed 1 month posttreatment; ***Based on symptoms or glucose breath test results; ****p < 0.01; *****p < 0.05; ******Based on lactulose breath test results; *******p < 0.02; ********p = 0.03; sustained for 10 days posttreatment; *********Based on Rome I criteria; **********p = 0.02.
Hydrogen excretion from baseline levels was correlated with improvement in bloating and overall symptom scores (p = 0.01 for both) (22). Interestingly, none of the patients in this study had abnormal breath test results at baseline, suggesting that rifaximin improves symptoms in the absence of SIBO (22).

To investigate the efficacy of rifaximin in treating IBS, a subanalysis of a randomized, placebo-controlled study (22) was conducted for the 70 patients who met Rome II criteria for IBS (22). A significantly higher percentage of patients who received rifaximin 800 mg/day reported symptom improvement compared with those who received placebo (40% of 37 vs 18% of 33 patients, respectively); this positive effect was sustained for at least 10 days posttreatment (22).

In addition, in a randomized, double-blind study of 87 patients with IBS, rifaximin 1,200 mg/day for 10 days significantly improved bloating (p < 0.001) and global IBS symptoms (p = 0.02) compared with placebo (Table 2) (23). These benefits were sustained up to 10 weeks posttreatment (Figure 1), suggesting that chronic antibiotic treatment may not be necessary for sustained clinical benefit and that rifaximin may affect a causal mechanism of IBS (23).

**Safety profile.** Because rifaximin is minimally (<0.4%) absorbed, it is not likely to be associated with systemic adverse effects. In the studies presented in this review that reported safety data, rifaximin administered for up to 14 days was well tolerated (19–23,40). In many of these studies, no drug-related adverse effects were observed (20–22,40). The adverse effects that were reported (e.g., abdominal pain, weakness, headache, constipation) were mild (19,23), and the incidence did not differ from placebo (23). Rifaximin has also exhibited favorable safety and tolerability in short-term studies of travelers’ diarrhea (38) as well as in longer duration studies of pouchitis remission maintenance during which patients received daily rifaximin treatment for at least 3 months (45).

Unlike systemic antibiotics, rifaximin has not been associated with clinically relevant antimicrobial
resistance during approximately 20 years of availability in Europe (37), and a study of patients with SIBO has shown rifaximin to be associated with fewer adverse effects than levofloxacin or metronidazole (42). Because rifaximin is only minimally absorbed, drug interactions with systemically absorbed medications are unlikely. Rifaximin does not induce or inhibit key cytochrome P450 enzymes in vitro and has shown no clinical evidence of interacting with drugs metabolized by these enzyme systems (38). Rifaximin 600 mg/day has also shown a lack of systemic accumulation with repeated administration for up to 3 days (38).

Neomycin

Neomycin is an oral aminoglycoside antibiotic that is absorbed into the systemic circulation. The efficacy of neomycin has been shown in a randomized, double-blind study with 111 patients who met Rome I criteria for IBS (10). In a subanalysis of the 93 patients (84%) with abnormal breath test results at baseline, 46% of patients who received neomycin 1 g/day for 10 days (n = 46) had a clinical response compared with 15% of those who received placebo (n = 47; p < 0.01). Only 8 (20%) of the 41 patients treated with neomycin who had abnormal breath test results at baseline and complete study data achieved a normal breath test result. Of the 84 patients with an abnormal breath test result at baseline and complete study data, the percent improvement in composite symptom scores was greatest among patients who had breath test result normalization with neomycin (62% ± 9%), followed by those whose breath test results were not normalized with neomycin (34% ± 6%) and those who received placebo (4% ± 12%; p = 0.01) (10). In a subanalysis of patients with constipation-predominant IBS from the Pimentel, et al (10) study, neomycin 1 g/day for 10 days resulted in greater global symptom improvement compared with placebo (44% ± 8% vs 6% ± 4%, respectively; p < 0.001) (34). The percent improvement in symptoms was greater in patients who excreted high levels of methane in lactulose breath testing compared with those who excreted high levels of hydrogen (68% ± 6% vs 33% ± 10%, respectively; p < 0.05), supporting the potential involvement of increased methane production in patients with constipation (34).

Safety profile. In the study conducted by Pimentel, et al (10), no drug-related adverse effects were reported following 10 days of treatment with neomycin. However, neomycin may be associated with potentially serious adverse effects, including delayed-onset ototoxicity that may lead to hearing loss, muscle-related neurotoxicity, and nephrotoxicity. Neomycin has also been shown to inhibit the absorption of some drugs (e.g., penicillin, digoxin, and methotrexate) and enhance the effect of others (e.g., anticoagulants). As with other systemic antibiotics, antimicrobial resistance and development of Clostridium difficile colitis are potential concerns.

Other Systemic Antibiotics

Several other systemic antibiotics, including metronidazole, ciprofloxacin, and chlorotetracycline, have been evaluated for efficacy in treating SIBO or IBS, but the limited published data available concern primarily patients with SIBO. In a study of 21 patients with blind loop syndrome and SIBO, metronidazole 500 mg/day for 7 days significantly reduced total hydrogen excretion compared with baseline levels (p < 0.001) and significantly improved symptom severity (p = 0.001) (46). Ciprofloxacin for the treatment of SIBO was reported in an open-label study of 12 patients with nonalcoholic steatohepatitis, six of whom had positive breath test results (47). Ciprofloxacin 1 g/day for 5 days normalized glucose breath test results for five of these six patients (p = 0.025) (47). In studies of patients with IBS and SIBO, antibiotic treatment with metronidazole, ciprofloxacin, neomycin, or doxycycline (n = 47) (11) or metronidazole, rifaximin, or fluoroquinolones (n = 64) (12) significantly improved breath test results (p < 0.0001 and p < 0.01, respectively) (11,12) and reduced the number of patients with abdominal pain (p < 0.001) and diarrhea (p < 0.001) (11). However, specific benefits of individual antibiotics were not reported in these studies; therefore, no conclusions can be drawn about the efficacy and safety of metronidazole or ciprofloxacin (11,12). In a study of patients with SIBO, chlorotetracycline 1 g/day for 7 days did not improve breath test results for fasting, peak, or total hydrogen excretion compared with baseline measures and did not improve symptom scores for
Bacteria and the Role of Antibiotics in IBS

diarrhea, borborygmi, or lassitude compared with baseline levels (20). Chlorotetracycline normalized breath test results in only 3 (27%) of 11 patients (20).

CONCLUSIONS
Emerging evidence suggests that bacteria, specifically overgrowth of colonic bacteria in the small intestine, may play a pathogenic role in IBS. The hypothesized involvement of SIBO in IBS provides a potential explanation for symptoms, such as bloating and increased gas production, experienced by many patients with IBS. The efficacy of antibiotics for reducing gas excretion and relieving symptoms associated with gas production supports the involvement of intestinal bacteria in IBS. Among antibiotics currently available, rifaximin has been most extensively evaluated for the treatment of SIBO and IBS. In contrast to systemic antibiotics, no clinically relevant antimicrobial resistance has been reported with rifaximin, and the low (<0.4%) absorption profile of rifaximin suggests a minimal risk of systemic adverse effects. Although further research is needed, the sustained clinical benefit reported following a short course of rifaximin suggests that antibiotic therapy may address a causative mechanism underlying some manifestations of IBS. Additional studies are warranted to more fully elucidate the putative role of intestinal bacteria in the pathophysiology of IBS and the potential therapeutic benefit of antibiotics in treating IBS. ■

References
Bacteria and the Role of Antibiotics in IBS


