

# A Combination of Rifaximin and Neomycin Is Most Effective in Treating Irritable Bowel Syndrome Patients With Methane on Lactulose Breath Test

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**Aim:** There is a growing interest in methane and its association with constipation in functional bowel disease. Neomycin-based treatment of methane-positive subjects has resulted in improvement of constipation. Rifaximin, although superior for the treatment of irritable bowel syndrome compared with other antibiotics, seems less effective in methane-positive subjects. In this study, we evaluate 3 different antibiotic treatments in patients who have a methane-positive breath test: rifaximin only, neomycin only, and the combination of neomycin and rifaximin.

**Methods:** A retrospective chart review was conducted on patients with methane on their lactulose breath test ( $\geq 3$  ppm of methane) who received one of the following antibiotic treatments: 500 mg b.i.d. for 10 days of neomycin alone, 400 mg t.i.d. for 10 days of rifaximin alone, or a combination of both rifaximin and neomycin for 10 days. All patients must have received antibiotic treatment after their initial consultation at the medical center and, in addition, had at least 1 follow-up to evaluate the effects of the treatment. After inclusion/exclusion criteria were met, all charts were evaluated to determine if the subject was a responder to the antibiotic therapy. This included clinical symptom improvement and eradication of methane on their breath test.

**Results:** Of the subjects receiving the treatment of rifaximin and neomycin ( $n = 27$ ), 85% had a clinical response, compared with 63% of subjects in the neomycin only group ( $n = 8$ ) ( $P = 0.15$ ) and 56% of subjects in the rifaximin only group ( $n = 39$ ) ( $P = 0.01$ ). When comparing the neomycin group with the rifaximin group, the difference was nonsignificant. When evaluating methane eradication results, 87% of subjects taking the rifaximin and neomycin combination eradicated the methane on their breath test. This is compared with 33% of subjects in the neomycin group that eradicated the methane ( $P = 0.001$ ), and only 28% of subjects in the rifaximin group ( $P = 0.001$ ). Of the patients who did not eliminate the methane with only rifaximin treatment, 66% of those who subsequently used the rifaximin and neomycin treatment were able to normalize their breath test.

**Conclusions:** The combination of rifaximin and neomycin is more effective in treating methane-producing subjects—in both clinical response and methane elimination.

**Key Words:** IBS, methane, constipation, antibiotics

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Irritable bowel syndrome (IBS) is a functional disorder characterized by recurrent abdominal pain and altered bowel habits, along with a constellation of other symptoms such as gas, bloating, incomplete evacuation, and relief of abdominal pain with defecation. IBS has been known to affect up to 20% of a given population.<sup>1,2</sup> Furthermore, IBS affects the quality of life of all age groups and is seen to be more common in women.<sup>2</sup> Irritable bowel patients have been classified into 3 different categories: diarrhea-predominant IBS, constipation-predominant IBS (C-IBS), or IBS with mixed bowel habit, patients who experience episodes of both constipation and diarrhea. In the case of C-IBS, it is believed to affect approximately one-third of the IBS population.<sup>3</sup>

Many new hypotheses have been proposed to explain IBS. More recently, IBS has been linked to an excess amount of bacteria in the small intestine; this is known as small intestinal bacterial overgrowth (SIBO).<sup>4</sup> Subjects with SIBO have similar symptoms to IBS, such as bloating, abdominal pain, and altered bowel habits.<sup>5</sup> In addition, a recent small bowel culture study found increased coliform bacteria counts in IBS subjects when compared with controls.<sup>6</sup> Although the authors did not find that the IBS subjects met the standard criteria for SIBO, defined as  $> 10^5$  cfu/mL, 43% of IBS subjects had increased coliform ( $\geq 5 \times 10^3$ /mL) compared with 12% in controls.

Diagnosing SIBO is a very difficult and controversial issue; there is no gold standard. This is partly due to the fact that the etiology still remains unknown. SIBO may be diagnosed by a noninvasive breath test. However, this is an indirect measure of bacterial overgrowth testing, which can be problematic. Through lactulose fermentation, bacteria produce gases such as hydrogen and methane. Bacterial fermentation is the only source of these gases in humans. Therefore, elevated levels of the gases early on in the breath test suggest the presence of bacterial overgrowth. It has been reported that 78% of subjects with IBS have a positive lactulose breath test (LBT), suggesting the presence of SIBO.<sup>6</sup> In addition to the hypothesized association between IBS and SIBO, recent studies have confirmed a high correlation between C-IBS patients and the presence of methane on LBT.<sup>3,7,8</sup> In fact, most IBS patients who produce methane on their LBT are known to have C-IBS.<sup>6,7</sup> In further support of this concept, the degree of methane on the LBT also seems to correlate with the severity of the constipation.<sup>3</sup>

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In randomized controlled studies evaluating the use of antibiotics, they seem to improve IBS. In 1 trial, although neomycin improved IBS symptoms, it was seen to normalize the breath test only 20% of the time.<sup>7</sup> However, rifaximin, a gut-selective nonabsorbable antibiotic, had higher eradication rates in bacterial overgrowth. Eradication rates of bacterial overgrowth using rifaximin have been seen in as high as 70% of patients,<sup>9</sup> and in a recent controlled study, rifaximin improved IBS symptoms for up to 10 weeks after its discontinuation.<sup>10</sup> However, in a subanalysis of C-IBS subjects, neomycin seems to be effective in treating constipation, although improvement depended on neomycin eradicating methane on LBT.<sup>11</sup> Neomycin was no different from placebo among C-IBS subjects with no methane on LBT. Thus, looking at the presence or absence of methane on a breath test in C-IBS may be important in treating constipation with neomycin.

Although rifaximin is the most effective antibiotic in IBS, it has not been adequately studied in the treatment of subjects with methane on breath test. In this study, we aim to study the efficacy of neomycin, rifaximin, and the combination of neomycin and rifaximin in clinical symptom improvements of IBS and methane eradication among methane-positive IBS subjects.

## METHODS

### Subject Population

A retrospective chart review was conducted among consecutive subjects seen for consultation at a tertiary care Gastrointestinal Motility Program. These subjects met the Rome I criteria<sup>12</sup> for IBS. All subjects had a baseline LBT demonstrating the presence of methane. This was defined as having a methane concentration of 3 ppm or greater on any given reading during a 180-minute LBT. There were 3 types of antibiotic treatments evaluated; all subjects must have received at least 1 type of the following antibiotic treatment: 500 mg b.i.d. for 10 days of neomycin alone, 400 mg t.i.d. for 10 days of rifaximin alone, or a combination of both rifaximin and neomycin for 10 days. In general, the decision of which antibiotic to administer was based on the year. Before 2004, neomycin was the drug of choice. After 2004, rifaximin was the first choice and subsequently from 2007 to 2008, the preferred choice was the combination of neomycin and rifaximin. Through this time period, no other variables were different and the technology for assessing methane remained the same.

Subjects were excluded from the study if they had inflammatory bowel disease, unstable thyroid disease, bowel obstruction, documented pelvic floor dysfunction, or medications known to cause constipation (eg, narcotics, antidiarrheals, alosetron). In addition, subjects were excluded if their antibiotic treatment preceded their first consultation visit at the medical center or if they did not have a follow-up to evaluate the outcome of the antibiotic treatment.

### Data Extraction

Each subject's chart was reviewed to evaluate the subjects' demographics (age and sex), bowel symptoms, and medical history. These data were recorded from the subject's initial consultation chart notes. Baseline breath test results (hydrogen and methane) were recorded along with any follow-up (after treatment) breath tests. The type of antibiotic treatment (rifaximin, neomycin, or the combination of neomycin and rifaximin) and the clinical

response from it was also recorded. The follow-up clinical notes were examined to determine if the subject was clinically satisfied with their antibiotic treatment and if the antibiotic normalized the LBT, through eradicating the methane on the LBT. In most cases, subjects were seen within 2 weeks of completion of antibiotics.

### Data Analysis

The overall IBS improvement (clinical response) of the neomycin and rifaximin combination group was compared individually with the rifaximin only group and the neomycin only group. In addition, the rifaximin group was compared with the neomycin group. The same groups were compared for methane eradication on the breath test. Subjects who had a failed initial response to rifaximin and subsequently received rifaximin and neomycin combination treatment were also analyzed to evaluate their breath test normalization. These data evaluated the success of the neomycin and rifaximin combination antibiotic treatment in both clinical improvement and eradication of methane, when compared with rifaximin or neomycin alone. The study was approved by the institutional review board.

### Statistical Analysis

To compare the clinical response rates between groups, a Fisher exact test was used. The Fisher exact test was also used to evaluate the eradication of methane among groups. Significance was set at  $P < 0.05$ .

## RESULTS

### Study Subjects

A total of 119 subjects had a history of methane; however, after inclusion/exclusion criteria were met, a total of 69 subjects qualified for the chart review. Among these subjects, some received more than 1 type of antibiotic therapy; if this was the case, they were counted in multiple treatment groups. Therefore, a total of 8 subjects received neomycin only, 39 received rifaximin only, and 27 subjects received neomycin and rifaximin in combination. There was no significant difference in age and sex on comparison of all 3 groups (Table 1).

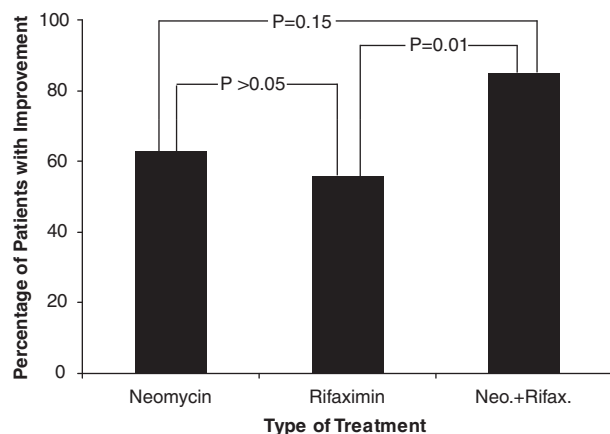
### Clinical Response

The combination of rifaximin and neomycin treatment was seen to have the highest clinical response when compared with the subjects taking rifaximin only, or neomycin only; 85% of subjects who received the neomycin and rifaximin combination had a clinical response ( $P = 0.01$  compared with rifaximin alone). Of the subjects receiving neomycin only, 63% had a clinical response to the therapy, whereas 56% of rifaximin only subjects responded clinically. There was no significant difference between rifaximin alone and neomycin alone (Fig. 1).

**TABLE 1.** Comparison of Age and Sex in the 3 Treatment Groups

	Age (Mean)	Female, n (%)
Neomycin (n = 8)	50.9 ± 18.3	7 (87.5)
Rifaximin (n = 39)	54.1 ± 17.8	26 (66.7)
Neomycin + Rifaximin (n = 27)	52.4 ± 14.1	18 (66.7)

There was no significant difference between the groups.



**FIGURE 1.** Comparison of the clinical response to the combination of rifaximin and neomycin.

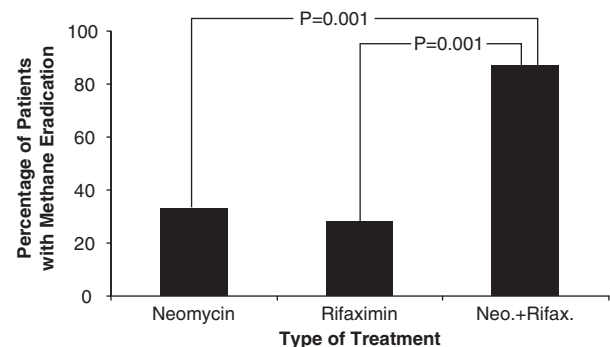
**Eradication of Methane**

Similar to the clinical response, the combination antibiotic therapy seemed to be most likely to eradicate methane on the breath test. In subjects who received neomycin alone, 33% eliminated methane on their follow-up breath test. This was not significantly different from the effects of rifaximin alone where rifaximin successfully eliminated methane in 28% of cases. However, the combination of rifaximin and neomycin was superior to single antibiotic therapy. In this case, the combination of the 2 antibiotics resulted in elimination of methane in 87% of cases (Fig. 2). This was significantly different from both single therapies ( $P < 0.001$ ).

Of note, 6 subjects who had failed to improve from the single antibiotic rifaximin were subsequently given rifaximin and neomycin. Despite failure with rifaximin alone, 4 of these cases (66%) receiving the combination of antibiotics were still able to eradicate methane.

**DISCUSSION**

In this study, we report the first use of combination antibiotic therapy directed specifically for methane-positive IBS subjects. Rifaximin is known to be effective in IBS<sup>10,13</sup> and very successful in normalizing the breath tests in those subjects with positive hydrogen profile on glucose breath test. However, clinical practice has observed that rifaximin



**FIGURE 2.** Comparison of the three treatment approaches in their ability, to eradicate methane based on postantibiotic breath test.

was not as effective in eliminating methane in subjects. In this study, we now demonstrate that the combination of rifaximin and neomycin seems highly effective for methane-positive subjects both in improving clinical response as well as eliminating methane.

There is now a growing body of literature that is unraveling the importance of methane in IBS, specifically in relationship to constipation. The initial descriptions of methane and its association with constipation suggest that almost all IBS subjects with methane on LBT seem to have symptoms consistent with constipation predominant IBS.<sup>8</sup> Since then, numerous groups have confirmed this relationship.<sup>7,14,15</sup>

Although demonstrating the association between methane and constipation is interesting, it does not inherently prove cause and effect. However, we have recently investigated the possibility that methane gas itself has an effect on bowel transit. In a live animal model of transit, the infusion of methane resulted in a 70% slowing of small intestinal transit.<sup>16</sup> It further appeared that methane had an active effect on transit by generating exaggerated motor activity in the small bowel and was associated with higher small bowel motility index in humans. Ironically, 2 previous studies showed whole gut and oro-cecal transit to be twice as long in humans with methane, compared with nonmethane subjects.<sup>17,18</sup>

The suggestion that methane may slow transit is important, as it opens the possibility of having a biomarker for constipation and may direct a therapeutic approach. To address the possibility that methane could be a biomarker for C-IBS, a blinded study was conducted, which demonstrated that the presence of methane had a sensitivity in predicting C-IBS of 92%.<sup>19</sup> Further proving a cause and effect relationship between methane and constipation, analyses of data from a double-blind study of neomycin in treating IBS demonstrated that neomycin improved constipation severity more than placebo.<sup>11</sup> However, the more important finding was that the entire improvement in constipation was dependent on the subjects having methane and subsequently eliminating methane successfully on their breath test.

With the evidence of methane to be a biomarker for constipation, this trait or finding can be used to track the effectiveness of a given therapy. As the degree of methane production on breath testing also correlates with the degree of constipation, therapies can be used to titrate the effect as well. In the current study, we aimed to determine the ideal therapy for elimination of methane. The 2 antibiotics that have demonstrated benefits in IBS through controlled trials are neomycin<sup>11</sup> and rifaximin.<sup>10</sup> Although data from Di Stefano et al,<sup>9</sup> suggest that rifaximin is a superior antibiotic for eradication of hydrogen on glucose breath testing, it has not been fully evaluated as a therapy for IBS subjects with methane. On the contrary, neomycin with a modest ability to normalize the breath test, has already demonstrated efficacy in the treatment of C-IBS, as discussed above.<sup>11</sup> In this study, we found that in fact, neomycin and rifaximin independently are only modestly effective in eradicating methane. However, the combination of neomycin and rifaximin is a superior treatment both in terms of clinical response and methane eradication.

Although these results offer a possible new method of treating C-IBS on the basis of a combination of antibiotics, this paper has significant limitations. This is a single center study using a retrospective chart review. However, the concept of a biomarker in C-IBS that could direct therapy

is very tantalizing. The limitations of this study provoke the need for a larger scale controlled trial.

In conclusion, this is the first comparison of different antibiotic therapies in the treatment of methane in the context of IBS. This study suggests that rather than rifaximin alone (which has low efficacy in the case of methane), a combination of rifaximin and neomycin should be taken into consideration as a type of treatment.

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