

Antibiotics for the Treatment of Irritable Bowel Syndrome

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Abstract: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder with an estimated worldwide prevalence of 10–20%. IBS can be associated with severe gastrointestinal symptoms, including abdominal pain, bloating, and altered bowel function. Although the causes of IBS remain undefined, recent research has increasingly suggested roles for gut flora in IBS. These roles involve postinfectious IBS, which can occur after a single episode of acute gastroenteritis, and small intestinal bacterial overgrowth, in which elevated populations of aerobic and anaerobic bacteria cause abdominal pain and altered bowel function. More recently, potential roles for methanogens in contributing to IBS subtypes have also been identified. In this paper, we review the different mechanisms by which gut flora may contribute to IBS and also discuss the efficacy and safety of various antibiotic therapies for treating IBS symptoms.

Irritable bowel syndrome (IBS) is the most common gastrointestinal disorder worldwide, affecting 10–20% of the adult population.^{1,2} IBS is characterized by recurrent abdominal pain, bloating, altered bowel function (constipation, diarrhea, or both), and a myriad of gastrointestinal symptoms.^{3–8} Severe IBS can significantly reduce quality of life, disrupt activities of daily life, and result in exorbitant healthcare costs.^{9–12} IBS therapies have previously focused on dietary restriction and symptom-based treatments, including stool softeners and agents that promote gastrointestinal transit in constipation-predominant IBS (C-IBS) as well as tricyclic antidepressants and antikinetic agents in diarrhea-predominant IBS (D-IBS).^{13–17} Despite the prevalence of and extensive research on IBS, diagnosis of IBS is currently made primarily utilizing clinical criteria rather than biologic markers of a detectable organic cause.¹⁸ Moreover, due to the lack of specificity in these criteria, IBS remains a diagnosis of exclusion. The pathophysiology of IBS has historically been attributed to disturbances of the brain-gut axis, abnormal gastrointestinal motor function, visceral hypersensi-

Keywords

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tivity, psychosocial factors, autonomic dysfunction, and mucosal immune activation. Over the past decade, there has been an accumulation of data suggesting that gut flora has a role in IBS.¹⁹⁻²² This growing area of literature has led to new IBS treatment concepts involving the use of antibiotics.²³⁻²⁶

Gut Ecology in Irritable Bowel Syndrome

Recent and accumulating evidence has demonstrated that gut bacteria play an important role in the production of symptoms and possibly the pathogenesis of IBS. The human gut is an elaborate microbial ecosystem consisting of 500–1,000 unique species of bacteria that are established early in life.^{27,28} These flora are progressively altered throughout adulthood by exogenous factors (ie, dietary intake) and endogenous factors (ie, genetic predisposition).²⁹⁻³² Although it is important to consider possible confounding endogenous factors—such as gender, age, and family history—recent technological advancements have improved our ability to examine bacterial profiles of the human gut, subsequently increasing our capacity to identify and classify enteric bacteria.³³⁻³⁵ Exogenous influences—such as infection by pathogenic microorganisms—also affect gut flora.

While endogenous gut flora will be discussed in the context of IBS in this review, pathogenic bacteria have also been implicated in IBS. A recent meta-analysis revealed that the rate of IBS development after a single episode of acute gastroenteritis may be as high as 10%, and up to 57% of patients continue to have altered bowel function 6 years after recovery from the acute episode.^{36,37} For the first time, these data suggest a significant attributable causative factor in IBS that can be examined prospectively. In a new animal model of postinfectious IBS, it was shown that acute gastroenteritis due to a common pathogen implicated in postinfectious IBS in humans (*Campylobacter jejuni*) led to the development of altered stool consistency 3 months after clearance of the initial infection.³⁸ More interestingly, the altered stool form was associated with the development of small intestinal bacterial overgrowth (SIBO) in these rats.³⁹ Although postinfectious IBS is an area of great interest, it is beyond the scope of this paper.

Small Intestinal Bacterial Overgrowth

SIBO is a clinical condition characterized by an abnormally high population of both aerobic and anaerobic coliform bacteria ($>10^5$ cfu/mL). Several conditions predispose patients to the development of SIBO: anatomic obstruction, autonomic neuropathy, and surgical revi-

sion.⁴⁰ SIBO symptoms include abdominal pain, bloating, and altered bowel function.⁴¹

For most of this past decade, SIBO has been suggested as a possible mechanism of symptoms in a subset of IBS patients. Much of this work has been based on indirect methods of diagnosing SIBO such as breath testing. Although there has been much argument regarding breath testing and its accuracy for evaluating SIBO, 2 recent meta-analyses suggest that abnormal breath testing is more commonly seen in IBS patients compared to healthy controls.^{20,22} The meta-analysis by Ford and associates examined the available literature and the techniques used for interpretation of breath testing.²⁰ The discriminating ability of the breath test appeared to depend on the technique used to interpret the test. A more recent meta-analysis, in addition to having access to a greater number of newly published studies, examined all studies and those studies that were designed as age- and sex-matched. In this meta-analysis, the odds ratio (OR) was nearly 10 in favor of the breath test suggesting the presence of SIBO.²² The possibility that SIBO is an etiology of IBS is supported by the reduction of gastrointestinal symptoms upon eradication of SIBO (discussed below).

Despite these meta-analyses, breath testing is difficult and complex to interpret. As a result, investigators have begun evaluating small bowel flora via culture techniques. However, culture has a number of limitations, making it a poor gold standard.⁴² These limitations include the difficulty of accessing the distal small bowel, inability to culture most intestinal microorganisms, contamination by oral flora, and vigorous growth of anaerobes. However, 2 studies have examined the coliform level in the proximal bowel of IBS patients. These studies have demonstrated that IBS subjects have a significantly higher number of coliforms in their small bowel compared to healthy controls and even compared to subjects with upper gastrointestinal illness that warrants esophagogastroduodenoscopy.^{19,21}

A recent publication set forth a modification of Koch's postulates to illustrate that SIBO is a potential cause of IBS symptoms.⁴³ This exercise made the following conclusions: Evidence indicates the presence of excessively high numbers of coliforms in the small bowels of IBS patients; data demonstrate a high prevalence of SIBO in IBS, based on abnormal breath testing (although a valid definition of SIBO based on culture is debatable); eradication of SIBO results in significant relief of IBS symptoms; and recurrence of SIBO corresponds with the return of IBS symptoms.^{20,22,44} This relationship was confirmed by a study conducted by Lauritano and colleagues in which 43.7% of subjects experienced recurrence of SIBO as assessed by

Table 1. Evidence Supporting the Relationship Between Methane and Constipation-Predominant Irritable Bowel Syndrome (C-IBS)

Evidence	Reference(s)
The presence of methane is associated with C-IBS.	<ul style="list-style-type: none"> • Thompson WG, Longstreth GF, Drossman DA, et al⁸⁹ • Holt PR⁵¹ • Pimentel M, Chow EJ, Lin HC⁵² • Pimentel M, Mayer AG, Park S, et al⁴⁸ • Chatterjee S, Park S, Low K, et al⁶⁴ • Shah ED, Basseri RJ, Chong K, Pimentel M²²
Constipation severity (subjective) is proportional to the degree of methane produced.	<ul style="list-style-type: none"> • Pimentel M, Chow EJ, Lin HC⁵² • Pimentel M, Mayer AG, Park S, et al⁴⁸
Constipation severity (objective) is proportional to the degree of methane produced.	<ul style="list-style-type: none"> • Chatterjee S, Park S, Low K, et al⁶⁴
The presence of methane is associated with slow transit.	<ul style="list-style-type: none"> • Cloarec D, Bornet F, Gouilloud S, et al⁶⁶ • Soares AC, Lederman HM, Fagundes-Neto U, de Morais MB⁶¹ • Stephen AM, Wiggins HS, Englyst HN, et al⁶⁸ • Pimentel M, Soffer EE, Chow EJ, et al⁹²
Infusion of methane into the small intestine slows transit.	<ul style="list-style-type: none"> • Pimentel M, Lin HC, Enayati P, et al⁵⁰
Eradication of methane via antibiotics improves constipation symptoms.	<ul style="list-style-type: none"> • Pimentel M, Chow EJ, Lin HC⁵² • Pimentel M, Chatterjee S, Chow EJ, et al²³ • Pimentel M, Chow EJ, Lin HC⁷⁵ • Sharara AI, Aoun E, Abdul-Baki H, et al²⁵ • Pimentel M, Park S, Mirocha J, et al²⁴

breath testing after 9 months, with concomitant recurrence of gastrointestinal symptoms.⁴⁵

Methane

An interesting aspect of breath testing has involved the relationship between gases measured via clinical testing and symptoms. This is most evident in the relationship between methane and the IBS subgroups. Increased methane on breath test correlates with constipation in IBS. Previously thought to be inert, methane gas is produced by methanogenic archaea, which are extremely fastidious and difficult to culture. The most common methanogenic colonizer of humans is *Methanobrevibacter smithii*.^{46,47} Among studies of breath testing in functional disease, methane on breath test is associated with constipation phenotypes including C-IBS and constipating conditions (such as encopresis and diverticulosis) and is less prevalent in diarrheal conditions.⁴⁷⁻⁴⁹ Recently, our group demonstrated that methane gas, as produced by gut bacteria, was able to slow small intestinal transit by 59% in an in vivo model of transit.⁵⁰ This finding suggests that methane has an active role in the development of constipation. These data further suggest that methanogens and methane production may have

a cause-and-effect relationship with constipation. Data supporting this relationship are outlined in Table 1. In the first study of IBS and breath testing, the majority of IBS patients producing methane appeared to have C-IBS.⁵¹ A 2003 study recognized that methane on breath test was associated with a constipation phenotype, as methane excretors had a mean constipation score nearly double that of nonmethane excretors.⁵² In fact, all 12 patients with C-IBS had methane detected via breath testing. In a large retrospective analysis, there was a significant association between the severity of reported constipation and the presence of methane, whereas the opposite was true for diarrhea.⁴⁸ Furthermore, if a breath test demonstrated methane positivity, this finding was associated with C-IBS.

Although methane appears to be associated with, and perhaps contributes to, constipation, what is more important is that it may identify a subgroup of IBS patients who respond to a specific therapy directed at eliminating or reducing the production of this gas. We recently conducted a systematic review of the literature and performed a meta-analysis to examine the cumulative evidence supporting the association between methane and constipation.⁵³ Comparison of the prevalence of methane (based on breath testing via gas chromatography) in a popula-

tion with and without constipation as the predominating symptom (including C-IBS and/or functional constipation) was required for inclusion in the final analysis. Nine studies met these inclusion criteria, and the presence of methane was more often associated with a constipation phenotype (OR, 3.51; CI, 2.00–6.16).^{48,52,54-60} In addition, the systematic review identified 8 papers that examined intestinal transit in the presence of methane using different techniques (orocecal, colonic, and whole-gut transit time; bowel frequency), which demonstrated that the presence of methane was associated with significant slowing of intestinal transit, irrespective of the method used to measure intestinal transit.⁶¹⁻⁶⁸

Antibiotics Used to Treat Irritable Bowel Syndrome

Evidence of the involvement of bacteria in IBS provides a rationale for the potential therapeutic benefit of antibiotic treatment. Several studies have shown that systemic antibiotics eradicate SIBO and improve bowel symptoms.²³⁻²⁶ These observations have been the basis for a series of controlled studies investigating the efficacy of various antibiotic treatments for IBS. As SIBO consists of aerobic and anaerobic bacteria (both gram-positive and gram-negative), treatment would ideally entail a broad-spectrum antibiotic with a minimal side-effect profile and low resistance.

Several broad-spectrum absorbable antibiotics have successfully reduced overgrowth: tetracycline, amoxicillin clavulanate (Augmentin), metronidazole (Flagyl), and fluoroquinolones (such as norfloxacin); however, these drugs are not without systemic side effects.^{69,70} As a result, nonabsorbable/topical antibiotics that act strictly on the gut lumen have been utilized to avoid systemic side effects by selectively eradicating gut flora. Rifaximin (Xifaxan, Salix) has been shown to be effective, has a low incidence of resistance, and has few serious side effects.⁷¹⁻⁷⁴

Neomycin

Clinical studies have demonstrated that the reduction or elimination of SIBO with antibiotic treatment alleviates IBS symptoms. Initial descriptions of antibiotic benefits in IBS used neomycin as the therapeutic agent. In a single, double-blind, randomized, controlled trial of 111 patients, neomycin-treated patients were more likely to experience a 50% improvement in global IBS symptoms compared to placebo-treated patients (43% vs 23%; $P < .05$).⁵⁹ In this study, 78% of IBS patients had an abnormal lactulose breath test result consistent with SIBO, and eradication of SIBO with neomycin led to an even greater response rate.⁷⁵

However, using neomycin as a therapy for IBS poses several challenges. First, in the previously mentioned

double-blind study, 25% of subjects who took neomycin failed to normalize their breath test abnormalities. Second, neomycin produces rapid and durable evidence of clinical resistance. In a recent study, 75% of subjects who took conventional antibiotics such as neomycin did not respond to subsequent therapy.⁷¹ Although data on neomycin are historically interesting as part of the initial examination of the role of gut bacteria in IBS, this antibiotic does not have the ideal properties needed to facilitate a gut-flora treatment approach to IBS.

Despite data that support the efficacy of conventional antibiotics such as neomycin for treating SIBO and IBS, administration of these drugs is limited by issues such as clinical resistance.^{59,76} An ideal antibiotic for a condition such as IBS would need to be nonabsorbable, be effective at improving IBS symptoms, and have gut specificity, a low bacterial resistance profile, no or limited side effects, and broad-spectrum coverage.

Rifaximin

Rifaximin is a semisynthetic, antibacterial, rifamycin derivative with virtually no systemic absorption and a favorable side-effect profile.⁷⁷ Rifaximin acts by binding to the β -subunit of bacterial DNA-dependent RNA polymerase—resulting in inhibition of bacterial RNA synthesis—and rifaximin has activity against a variety of enteric bacteria.⁷⁸⁻⁸¹ This drug exhibits activity against both gram-positive and gram-negative aerobes and anaerobes.^{73,82} Initially, rifaximin was investigated for the treatment of SIBO.^{76,83}

In 4 clinical trials, rifaximin demonstrated effects against human pathogenic infection (traveler's diarrhea), for which it currently has a US Food and Drug Administration (FDA) indication.^{76,83-85} Recently, rifaximin received a second indication for hepatic encephalopathy on the basis of its safety and efficacy in a population of individuals with end-stage liver disease.^{86,87} However, at present, rifaximin is not approved by the FDA for the treatment of IBS.

In addition to its beneficial safety profile and antimicrobial characteristics, rifaximin has demonstrated a significant benefit for treating SIBO based on breath tests. In a prospective, randomized trial of 90 patients, Lauritano and coworkers demonstrated the efficacy of rifaximin for SIBO eradication by showing normalization of abnormal glucose breath test findings in IBS subjects.⁸⁸ Due to its properties, rifaximin was subsequently examined for treatment of IBS. The first study examining the use of rifaximin in IBS was a 2-center, randomized, controlled study of 87 subjects.²⁴ This study demonstrated that rifaximin was superior to placebo for improving IBS after only 10 days of treatment. The study also revealed a durable benefit when subjects were followed for 10 additional weeks. This finding was

unique among drugs used to treat IBS and suggested that rifaximin was addressing a potential causative factor in the condition. These results have since been replicated in several controlled trials.²⁴⁻²⁶

To date, the strongest evidence supporting the role of rifaximin in IBS consists of 2 large-scale, multicenter, phase III studies: TARGET 1 and TARGET 2.²⁶ In these identically designed studies, subjects with nonconstipated IBS of mild-to-moderate severity received rifaximin 550 mg 3 times per day or matching placebo for 14 days. After the conclusion of therapy, subjects were followed for an additional 10 weeks. Daily and weekly symptoms were recorded for the duration of follow-up. The primary endpoint of the study was adequate relief of IBS symptoms for at least 2 of the first 4 weeks of follow-up. Adequate relief of bloating, a key secondary endpoint, was similarly evaluated. A total of 1,258 subjects were recruited into the 2 studies (n=623 for TARGET 1 and n=637 for TARGET 2). In both studies, a significantly greater percentage of patients receiving rifaximin 550 mg TID (41%) reported adequate relief compared to patients receiving placebo (31%; $P<.001$).²⁶ Rifaximin also demonstrated durability in treatment, in that improvement was seen over most of the 12 weeks of post-treatment symptom evaluation for adequate relief and bloating.

While the benefits of rifaximin seen in this study were significant, it is also important that there was no evidence of adverse events that exceeded those seen in the placebo group.²⁶ Furthermore, no cases of *Clostridium difficile* infection have been seen in any of the studies of rifaximin in IBS.

Although rifaximin has demonstrable benefit in non-C-IBS, there is some optimism regarding its use in C-IBS as well. The gut flora of C-IBS may, however, be different, as noted earlier. There is a propensity to observe methanogen colonization in C-IBS, as demonstrated by breath tests.^{48,51,59,89} One study noted that neomycin was successful at improving C-IBS that was dictated by the eradication of methane.²³ A subsequent retrospective chart review demonstrated that, unlike conventional SIBO, subjects with excessive methane via breath testing did not respond well to rifaximin or neomycin. However, combining the 2 antibiotics resulted in a greater-than-80% clearance of methane via breath testing with a similar clinical response.⁴⁸

Re-Treatment

Recently, there has been increasing interest in the effects of rifaximin re-treatment in IBS, in order to gain an understanding of patients' response to repeated use. Until recently, only 1 study had examined this effect.⁷¹ This small-scale retrospective chart review demonstrated that

subjects who required re-treatment with rifaximin almost always responded to subsequent re-treatment.⁷¹ However, this study was conducted a number of years ago; thus, only a few subjects (N=16) were eligible for analysis, and only 3 total treatments were evaluable. Our group recently completed a large-scale, multiyear, retrospective chart review that confirms these results with more subjects and more re-treatments.⁹⁰ In this study, up to 5 treatments of rifaximin were examined in IBS subjects presenting in the absence of constipation and other bowel disorders. Interestingly, if initial treatment with rifaximin was successful, re-treatment with rifaximin was successful in more than 80% of subjects regardless of the number of treatments given. In addition, the average time between treatments did not change with subsequent re-treatment visits.⁹⁰ While this was a retrospective chart review and therefore has obvious limitations, it was a study of the "real-world" use of rifaximin for treatment of IBS.

As previously mentioned, although they are occasionally successful at improving IBS symptoms, conventional antibiotics for treating SIBO, such as neomycin, have been notable for the development of resistance. In fact, nearly 75% of subjects responding to neomycin initially failed to respond to re-treatment. Although a recent study by Valentin and associates found that 7 of 11 healthy volunteers developed rifampin-resistant staphylococci after taking rifaximin, we found no evidence of clinical resistance to rifaximin in IBS subjects over the course of up to 6 re-treatments.^{90,91}

Table 2. Rifaximin for Treatment of Irritable Bowel Syndrome (IBS): Summary of Key Points

- Consistent efficacy of rifaximin in treatment trials.
- Durable response after cessation of rifaximin therapy.
- No side effects with rifaximin, unlike other IBS therapies such as tricyclic antidepressants.
- No demonstrable absorption.
- Not needed to treat systemic life-threatening infections.
- Clinical resistance seen for other antibiotics but rarely for rifaximin.
- Re-treatment with rifaximin is successful compared to other antibiotics.
- No cases of *Clostridium difficile* infection in IBS clinical trials of rifaximin.
- Phase III studies demonstrate response in most symptoms of IBS with fewer numbers of subjects than previously approved drugs.

Conclusion

In the past decade, gut flora has demonstrated importance in IBS, and gut flora may contribute to symptoms in a subset of these subjects. Although breath testing appears to be more commonly abnormal in IBS based on meta-analysis, this test is imperfect for definitively identifying SIBO. However, culture studies suggest that a subset of IBS subjects have overgrowth of coliforms in the small bowel. Due to the lack of good indirect tests for SIBO and the invasive and challenging nature of small bowel culture, there is no good marker for SIBO in IBS, and this is likely to be the case for the foreseeable future. Nevertheless, the safety and mechanism of action of rifaximin has enabled success in the empiric treatment of D-IBS (Table 2). Re-treatment, while studied on only a small scale, appears effective.

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(Continued on page 493)

(Basseri et al, continued from page 460)

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