

EDITORIAL

Clin. Invest. (2011) 1(4), 479–482



"The role of small intestinal bacterial overgrowth in IBS has been the subject of considerable controversy ... casting some doubt on its nigh ubiguity..."

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Antibiotics in irritable bowel syndrome: a novel approach to a challenging disorder

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Irritable bowel syndrome (IBS) is a common and sometimes disabling syndrome that has been reported to affect up to 10–15% of adults in North America [1] and Western Europe [2]. As a result of its heterogeneous nature and undefined pathophysiology, progress in the management of IBS and its symptoms has been slow and has been further hampered by the withdrawal of promising new pharmacological agents due to what were considered unacceptable rates of adverse events. IBS has been barren ground for the pharmaceutical industry given the perception of regulatory agencies that it is a benign condition and, accordingly, drugs for the treatment of this disorder should be devoid of any serious side effects. Fortunately, this pharmacological drought has not deterred clinical investigators who have continued to pursue studies on the etiology of IBS; a journey that has taken investigators on some unexpected journeys and led to some intriguing hypotheses.

Gut microbiota & IBS: a basis for the use of antibiotics

Several phenomena undoubtedly contribute to symptom genesis in IBS, including disordered bowel motility ('spasm'), visceral hypersensitivity or hyperalgesia, altered cerebral processing of gut events, environmental stressors and intrinsic psychopathology. The interplay between such gut and CNS factors has led to the concept of gut-brain axis dysfunction as fundamental to the induction of symptoms in IBS. According to this concept and, putting it simply, the interaction or interplay between gut dysfunction and a central factor, such as stress or anxiety, leads to the development of symptoms. Another factor, food ingestion, is commonly invoked as the cause of symptom onset by patients with IBS and has led many in a vain search for food allergies and intolerances and others to experiment with functional foods. Indeed, many IBS sufferers had taken to ingesting products purporting to have prebiotic or probiotic properties long before clinical investigators either developed a rationale for their use in IBS or formally tested their efficacy in clinical trials. This approach has recently been given scientific credibility with reports, from a number of laboratories, of potentially related phenomena, namely, subtle alterations in immune function and disturbances in the composition of the intrinsic bacterial population of the gut (the enteric flora or microbiota) among selected IBS patients. The possibility that the enteric flora or microbiota could play a role in the pathogenesis of IBS has only very recently begun to attract concerted scientific attention, although evidence to suggest a link has been extant for some time and contains several distinct strands. These include: epidemiological evidence that antibiotic use may predispose to IBS or to exacerbations thereof [3], epidemiological, clinical and experimental evidence for the existence of postinfectious IBS [4], evidence, both experimental and clinical, for a role for low-grade inflammation and/or immune activation in IBS

Keywords: antibiotics • irritable bowel syndrome • microbiota • rifaximin • small intestinal bacterial overgrowth



and that such immune activation may be triggered by engagement with the microbiota [5], the suggestion that IBS may be associated with small intestinal bacterial overgrowth (SIBO) [6,7], or qualitative or quantitative changes in the colonic flora (dysbiosis) [8,9], and finally and perhaps most conclusively, evidence to indicate that manipulation of the gut flora, by antibiotics, probiotics or prebiotics, may ameliorate symptoms in IBS [10].

Postinfectious IBS

Despite the epidemiological evidence to link IBS with the use of antibiotics, an association that may reflect the use of antibiotics for severe enteric infections rather than an actual causative link, several lines of evidence have prompted an assessment of antibiotics in IBS. Firstly, the concept of postinfectious or postdysenteric IBS is now firmly established [4]. First noted by clinicians over 50 years ago, the occurrence of IBS following episodes of bacteriologically confirmed gastroenteritis has now been documented in several studies. Thabane and colleagues recently performed a systematic review and concluded that the overall risk for the development of IBS was increased sixfold following an episode of bacterial gastroenteritis. Younger subjects, those who have prolonged fever during the episode of gastroenteritis and those who suffer from anxiety or depression, were at greatest risk [11]. The nature of the infectious agent does not appear to confer additional risk. These symptoms are not transient with reasonably long-term studies documenting similar recovery rates for post-infectious and nonpost-infectious IBS. An important outcome of detailed studies of post-infectious IBS was to establish a direct link between prior exposure to an infectious agent, persisting low-grade inflammation and IBS; observations that critically, indicate a relationship between perturbations of the microbiota, mucosal inflammation and IBS, a hypothesis that is amply supported by data from studies in experimental animal models. Thus, although post-infectious IBS may explain only a minority of cases of IBS (probably <10%), it does represent a clear link between exposure to an environmental agent, such as a food-borne pathogen, inflammation and IBS in predisposed individuals. There is, as yet, no evidence to suggest that antibiotic therapy at the time of the initiating bacterial enteritis will diminish the likelihood of the subsequent development of post-infectious IBS; this question can only be resolved by a large prospective clinical trial, a daunting task given the low risk for progression to IBS after a given infection.

Small intestinal bacterial overgrowth

Although, perhaps mistakenly, antibiotics had been identified in population studies as a risk factor for the development of IBS, the suggestion that some IBS subjects might harbor SIBO led to clinical trials of these agents in this disorder. In a short-term study, the normalization of breath hydrogen excretion (taken to indicate the eradication of SIBO) by the administration of neomycin, led to symptom relief [7]. In a subsequent study that did not document bacterial overgrowth, Pimentel and colleagues treated IBS patients with the poorly absorbed antibiotic rifaximin [12], some IBS patients demonstrated a prolonged response (up to 10 weeks) to a short course of this antibiotic. The role of SIBO in IBS has been the subject of considerable controversy with other studies employing a variety of methodologies, as well as a recent systematic review [13], casting some doubt on its nigh ubiquity, as suggested by earlier studies [6,7].

Qualitative or quantitative changes in the colonic microbiota

The colon contains the most abundant and diverse bacterial population in the gastrointestinal tract, a population that performs several important biological functions for the host: the deconjugation of bile acids, the fermentation of undigested carbohydrates to produce various gases and the production of short chain fatty acids, essential fuels for the colon. Changes in the relative numbers of various bacterial species in the colon could alter the normal homeostatic relationship between microbiota and host and produce gastrointestinal symptomatology. For example, excessive deconjugation of bile acids will result in diarrhea and enhanced fermentation will produce flatulence and distension. Although our knowledge of the status of the colonic microbiota in IBS remains sketchy, in part related to inadequacies in the methodology of earlier studies and also to the microbiological and analytical challenges that the full description of such a complex ecosystem presents, some recent studies, using modern molecular methods, suggest that the colonic microbiota is altered in IBS [8,9]. Effects on the colonic microbiota could also explain the beneficial effects of antibiotics in IBS. Indeed, the eradication of SIBO, as initially proposed, may not be the sole explanation for these responses, which could also be explained on the basis of a suppression of fermenting bacteria in the colon. Thus, Sharara and colleagues showed that a positive effect of rifaximin on such symptoms as bloating was not dependent on having an abnormal lactulose breath hydrogen test at baseline [14]. Their demonstration, nevertheless, of a reduction in the area under the breath-hydrogen curve of responders would also support an effect on colonic fermentation.

Antibiotics in IBS: the evidence

Based, first, on enthusiasm for the concept of bacterial overgrowth in IBS and, second, on the aforementioned Phase IIa study of rifaximin [12], recent large studies have focused on the impact of this antibiotic. This antibiotic is viewed as especially appropriate for use in IBS, given the fact that it undergoes minimal, if any, systemic absorption and, to date, has not been associated with antibiotic-associated diarrhea or the emergence of *Clostridium difficile* colitis or carriage.

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In a multicenter Phase II study (to date reported in abstract form only), 388 diarrhea-associated IBS subjects were randomized to either rifaximin in a dose of 550 mg twice a day or placebo for 14 days, followed by another 14 days on placebo alone and then 2 weeks follow-up. During treatment, at 4 and 12 weeks, those randomized to rifaximin had a modest 8-13% therapeutic gain for adequate relief of global IBS symptoms and a rather disappointing 4-8% gain for relief of bloating [15,16]. These encouraging results have been reproduced and even bettered in two large multicenter Phase III trials, which have been published together [17]. These TARGET trials, involving a total of 1260 patients with non-constipated IBS in the USA and Canada showed a 9% therapeutic gain for adequate relief of IBS symptoms (the primary end point) and a 9.9% therapeutic gain for adequate relief of bloating (the key secondary end point) for rifaximin in a dose of 550 mg three-times daily over placebo [17]. Significant benefits were also seen for other secondary end points, such as abdominal pain and discomfort, loose or watery stools and stool consistency. Follow-up through 12 weeks (i.e., 10 weeks after the end of rifaximin therapy) indicated a continued benefit for those randomized to rifaximin with the effect on global IBS symptoms, although declining somewhat in magnitude, remaining statistically significant. Similar trends were observed for other end points. The frequency and nature of side effects were similar for the rifaximin and placebo groups. The frequencies of diarrhea and nausea were similar in both treatment groups and no instances of C. difficile associated diarrhea or ischemic colitis were recorded.

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Future perspective

The results of these large well-designed studies provide compelling evidence for a real effect both in the short term (i.e., 2-4 weeks) and, most intriguing and uniquely, in the medium term (10–12 weeks) of a short 10-14 day course of this antibiotic in IBS. The consistency of the data emanating from these rifaximin trials notwithstanding, one must remain reluctant, pending long-term studies, to recommend a prolonged course of antibiotic therapy to any population regardless of the safety profile of a given antibiotic. The dose of rifaximin has varied in these studies from 1100 to 1650 mg/day and for a disorder as chronic and relapsing as IBS, the duration of observation was rather short. It needs to be remembered as well that relapse rates following discontinuation of rifaximin therapy (while not documented in IBS) are high among patients with small intestinal bacterial overgrowth [18] and while such recurrences can be treated successfully by further courses of antibiotic [19], the advisability of repeated courses of antibiotics in any condition must be questioned, given the, at least theoretical, risks of *C. difficile* and antibiotic resistance.

Nevertheless, the consistency of these, albeit modest, effects of this antibiotic on IBS symptomatology is compelling and demands that we address several questions. How is it mediating these benefits – through SIBO, an impact on the colonic microbiota or an anti-inflammatory effect? Who are the responders and why do they respond? To date the focus has been on diarrhea predominant or nonconstipation IBS; bloating seems to be another predictor of response. What is the mechanism of action and where is this action exerted? The answers to these questions must provide valuable insights into IBS in general.

Financial & competing interests disclosure

The author has, in the past, been an advisor to Salix Pharmaceuticals and Norgine. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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