The place of antibiotics in management of irritable bowel syndrome: a systematic review and meta-analysis

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Submitted: 23 July 2009
Accepted: 21 August 2009

Arch Med Sci 2010; 6, 1: 49-55
DOI 10.5114/aoms.2010.13507

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Abstract

Introduction: Irritable bowel syndrome (IBS) is a prevalent gastrointestinal disease with an obscure pathophysiology. Current treatments for IBS have modest efficacy at best and the need for a robust therapy for IBS remains unmet. As small intestinal bacterial overgrowth has been proposed to be involved in pathogenesis of IBS, antibacterial agents might be efficacious in treatment of this condition.

Material and methods: PubMed, Embase, Scopus, Google Scholar, Web of Science, and Cochrane Central Register of Controlled Trials were searched for studies comparing the efficacy of antibiotics in the management of IBS and/or IBS type symptoms. Data were collected from 1966 to April 2009. Clinical response was considered as our key outcome of interest.

Results: Of five trials that evaluated the effect of antibiotics in IBS, two randomized placebo-controlled trials met the inclusion criteria for the meta-analysis. This meta-analysis included 234 patients with IBS-type symptoms of whom 181 met the Rome criteria for IBS. The pooled relative risk (RR) for "clinical response in IBS" was 2.04 (95% confidence interval [CI] of 1.23-3.40, $p = 0.0061$). The pooled RR for "clinical response in IBS-type symptoms" was 2.06 (95% CI of 1.3-3.27, $p = 0.002$).

Conclusions: Although antibiotics have a statistically significant effect on IBS and bloating, given the evidence for the presence of publication bias, methodological variability of the trials and lack of a precise scientific explanation for the role of bacterial overgrowth in the pathophysiology of IBS, use of antibiotics on a regular basis in IBS patients is not recommended.

Key words: irritable bowel syndrome, antibiotics.

Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder characterized by chronic or recurrent abdominal pain and discomfort associated with altered and alternating bowel habits. In addition, IBS patients commonly complain of abdominal bloating, flatulence, dyspepsia and incomplete evacuation [1].

Irritable bowel syndrome is present in up to 20% of the North American population [2] and inflicts a significant impact on the health care system [3].

The pathophysiology of IBS remains obscure. Environmental factors (psychological disturbances and stress), genetic links, recent infection, food

intolerance, altered bowel motility and/or secretion, visceral hypersensitivity, altered brain-gut sensory processing axis and enteric neuromuscular dysfunction are proposed as possible aetiological factors for IBS [2, 4, 5]. The beneficial effects of currently available approaches for management of IBS are modest at best and there is a true need to develop further efficacious therapeutic agents [6, 7].

Compared to the colon, the small bowel normally contains relatively few bacteria. Once the small bowel becomes populated by excessive bacteria (i.e. small intestinal bacterial overgrowth [SIBO]), it leads to various non-specific symptoms such as bloating, flatulence, abdominal pain and watery diarrhoea [8]. These symptoms are shared in a proportion of IBS patients so one might contemplate that SIBO is implicated in the pathogenesis of IBS. Moreover, excessive intestinal gas has been radiographically illustrated in IBS patients [9], which might explain "bloating" as a prevalent clinical finding. This phenomenon might be a result of increased gas production secondary to bacterial fermentation in SIBO. Subsequently, several randomized controlled trials (RCTs) were conducted to evaluate the effect of intestinal bacterial eradication with antibiotic therapy in IBS patients [10-14].

As there is considerable controversy regarding the use of antibiotics in IBS, we conducted this study to systematically review and meta-analyze the efficacy of antibiotics in adults with IBS and IBS-type symptoms in placebo-controlled trials.

Material and methods

PubMed, Embase, Google Scholar, Web of Science, and Cochrane Central Register of Controlled Trials were searched for studies that investigated efficacy of anti-bacterial agents in IBS. Data were collected from 1966 to April 2009. The search terms were: "anti-bacterial", "bacteriocidal", "antibiotics", "anti-mycobacterial", "rifaximin", "metronidazole", "vancomycin", "gentamicin", "cephalosporin", "neomycin", "norfloxacin", "amoxicillin-clavulanate", "irritable bowel", "functional bowel diseases" and "irritable colon". The search was restricted to English literature. Reference lists of the retrieved articles were also reviewed for additional applicable studies.

Controlled trials investigating the efficacy of antibiotics in patients with IBS were taken into consideration. Clinical response was the key outcome of interest for assessment of efficacy. We evaluated all the published studies as well as the abstracts presented at meetings. Two reviewers independently examined the title and abstract of each article to eliminate duplicates, reviews, case studies, and uncontrolled trials. For the meta-analysis, trials were disqualified if they were not placebo-controlled or outcomes were not dichotomized into responders and non-responders. Reviewers independently extracted data on patients' characteristics, therapeutic regimens, dosage, trial duration, and outcomes. Disagreements, if any, were resolved by consensus.

Jadad score, which evaluates studies based on their description of randomization, blinding, and dropouts (withdrawals), was used to assess the methodological quality of the trials [15]. The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

Data from selected studies were extracted into 2 × 2 tables. All included studies were weighted and pooled. Data analysis was done using StatsDirect (2.7.2). Relative risk (RR) and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenszel method. The Cochran Q test was used to test heterogeneity. In addition, a L'Abbe plot was used to explore the heterogeneity of effect estimates and the presence of publication bias.

Findings

The primary literature search yielded 92 studies from the aforementioned electronic databases. The process to select relevant studies is shown in Figure 1. Five RCTs were found to have evaluated the effect of antibiotics on IBS-type symptoms [10-14]. A study by Di Stefano *et al*. [14] compared the effect of antibiotics versus charcoal on gas

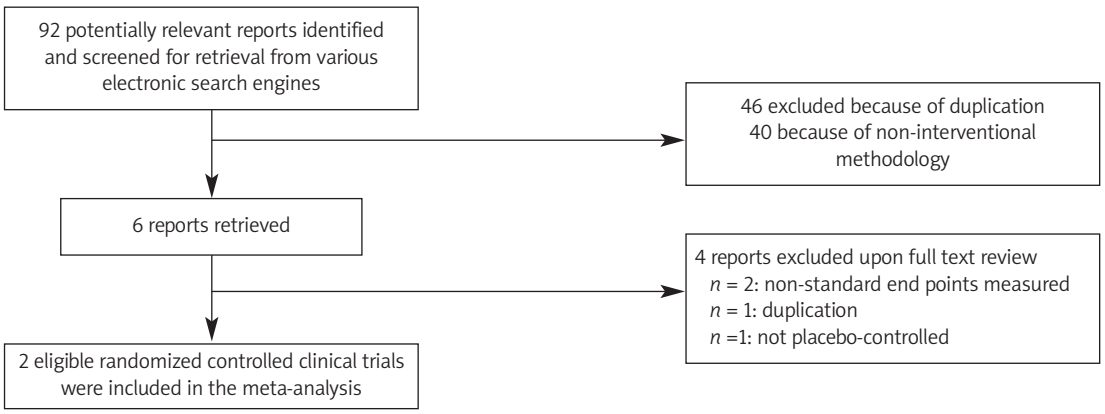

Figure 1. Flow diagram of the study selection process

production in patients with functional bowel disease. This study was excluded from our study as it did not have a placebo arm.

Jadad quality score, methodology and results of the remaining four RCTs are summarized in Tables I-III. Except for one study [10] data regarding subtypes of IBS (diarrhoea-predominant, constipated-predominant or alternating bowel habits) were not available. The primary outcome measure in the studies by Pimentel *et al.* [11] and Nayak *et al.* [12] was the average improvement in IBS composite clinical scores. As no conventional dichotomous data (responder vs. non-responder) were presented in these two studies, pooling the results with the other trials [10, 13] was not statistically possible. Various clinical composite scores were used in the trials (Table II); therefore, meta-analysis of the absolute change in the composite clinical scores was not practically possible.

Studies by Sharara *et al.* [13] and Pimentel *et al.* [10] were included in the final meta-analysis. As patients with IBS-type symptoms not meeting the Rome criteria were also included in the trial by Sharara *et al*. (Table II), the meta-analysis was conducted once with all the patients in Sharara's trial and once with only the IBS subgroup. This meta-analysis included 234 patients with IBS-type symptoms of whom 181 met the Rome criteria for IBS.

The pooled relative risk (RR) for "clinical response in IBS subgroup" [10, 13] was 2.04 (95% confidence interval [CI] of 1.23-3.40, p = 0.0061, Figure 2). Cochrane Q test suggested that the studies are homogeneous (p = 0.4937); however, given the small number of included studies, a random-effect model was used for the meta-analysis. Regression of normalized effect versus precision for all included

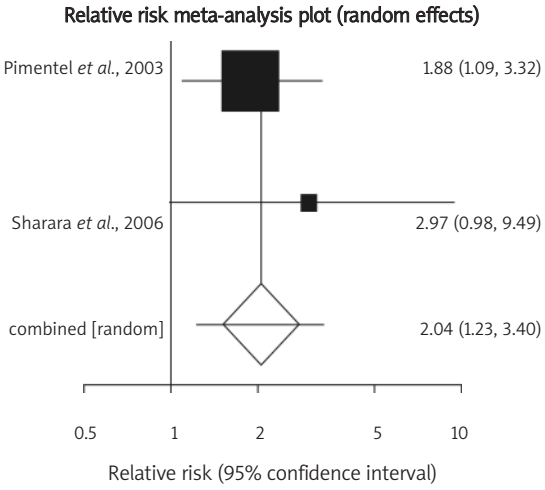

Figure 2. Individual and pooled relative risk for the outcome of "clinical response in IBS subgroup" in the studies considering antibiotic vs. placebo therapy

Table I. Jadad quality score of randomized controlled trials included in the meta-analysis

Study	Factors and Jadad score			
	Randomization	Blinding	Withdrawals and dropouts	Total Jadad score
Pimentel *et al.*, 2003	1	2	1	4
Pimentel *et al.*, 2006	2	2	1	5
Nayak *et al*, 1997	1	1	1	3
Sharara *et al.*, 2006	2	2	1	5

Table II. Characteristics of papers included in the meta-analysis

Study (n)	Mean age	Sex		Loss of follow-up [%]	Criteria to diagnose IBS	Treatment	Duration of follow-up post-treatment
		Female	Male				
Pimentel *et al.*, 2003	43	61	50	9	Rome I	Neomycin 500 mg twice daily for 10 days	7 days
Pimentel *et al.*, 2006	39	58	29	8	Rome I	Rifaximin, 400 mg thrice daily for 10 days	10 weeks
Nayak *et al.*, 1997 (n = 30)	N/A	N/A	N/A	0	Manning	Metronidazole 400 mg thrice daily for 10 days	50 days
Sharara *et al.*, 2006	41	68	56	6	*	Rifaximin 400 mg twice daily for 10 days	10 days

† *Nayak et al. also included a third non-blinded arm (n = 15) treated with ispaghula, which provided better results in pain control, reduction of mucus in stool and rectosigmoid motility compared to metronidazole (results not shown)*

** Rome II criteria were met in 56% of patients. Patients with bloating for more than 12 weeks with any of the symptoms of chronic abdominal pain, disturbances in bowel movements or abnormal stool consistency were included in the study*

Table III. Summary of the effect of antibiotics in IBS trials

Study (antibiotic of choice)	Definition of response	Response		Response in patients with abnormal initial breath test		Improvement of the composite score within the first ten days post-treatment (% improvement ± SD)		Long-term improvement of the composite score (% improvement ± SD)	
		Antibiotic	Placebo	Antibiotic	Placebo	Antibiotic	Placebo	Antibiotic	Placebo
Pimentel *et al.*, 2003	≥ 50% improvement in a composite score calculated from abdominal pain, diarrhoea and constipation	24/55	13/56	21/46	7/47	¶ǰScores N/A (35 ±5.0%)	Scores N/A (11.4 ±9.3%)	NA	NA
Pimentel *et al.*, 2006	Improvement in IBS global score on a visual analogue scale	Binary data NA (Improvement: 41%)	Binary data NA (Improvement: 25%)	Not measured	Not measured	¶ǰScores N/A (41% ± ?)	Scores N/A (25% ± ?)	Scores N/A (36.4 ± 31.4%)	Scores N/A (21.0 ±22.08%)
Nayak *et al.*, 1997	Improvement in a composite score calculated from abdominal pain, frequency of stools, stool consistency, presence of mucus in stool and feeling of incomplete evacuation	Binary data NA (n = 15)	Binary data NA (n = 15)	Not measured	Not measured	24 ±2.6 → 21.9 ±3.0* (9%)	24.6 ±2.6 → 21.5 ±3.1 (12%)	24 ±2.6 → 10.9 ±3.3† (54.6%)	24.6 ±2.6 → 18.1 ±3.9 (26.4%)
Sharara *et al.*, 2006	Positive response to the question: "Do you consider that your symptoms have improved since starting the study drug?"	18/63 (IBS subgroup: 10/37)	7/61 (IBS subgroup: 3/33)	All patients had normal level of LHBT	All patients had normal level of LHBT	112.3 ±9.4 → 106.4 ±12.1‡ (5.2%)	112.5 ±11.8 → 111.4 ±13.2 (1.0%)	NA	NA

¶ǰ*measured at day 7 post-treatment, * measured at day 5 post-treatment, † measured at day 50 post-treatment, ‡ measured at day 10 post-treatment*

studies for clinical response among rifaximin vs. placebo therapy could not be calculated because of too few strata.

The pooled RR for "clinical response in IBS-type symptoms" was 2.06 (95% CI of 1.3-3.27, $p = 0.002$, Figure 3). Cochrane Q test suggested that the studies are homogeneous ($p = 0.5702$); however, given the small number of included studies, a random-effect model was used for the meta-analysis. Regression of normalized effect versus precision for all included studies for clinical response among antibiotics vs. placebo therapy could not be calculated because of too few strata. Funnel plots for the percentage of the improvements could not be drawn due to absence of the corresponding variances. None of the studies reported a significant difference in adverse events among various arms.

Discussion

To our knowledge this is the first meta-analysis of antibiotic therapy in IBS and IBS-type symptoms. Irritable bowel syndrome patients who receive antibiotics are two times more likely to experience a clinical response within the first 10 days of treatment compared to those who received placebo (Figure 2). Similar findings were observed in patients with IBS-type symptoms, mainly flatulence, who received antibiotics (Figure 3). These results are statistically significant; however, several factors must be considered to determine whether these results bear clinical significance or practical relevance.

As previously noted, the main assumption behind the possible effectiveness of antibiotics in IBS is the presence of intestinal bacterial overgrowth. However, this hypothesis has been subject to scepticism due to lack of scientific proof.

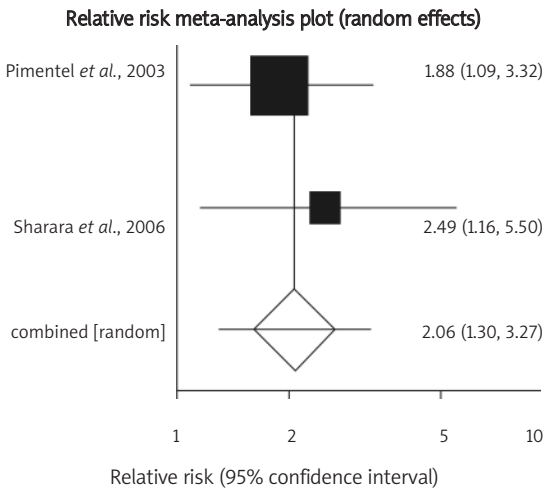

Figure 3. Individual and pooled relative risk for the outcome of "clinical response in IBS-type symptoms" in the studies considering antibiotic vs. placebo therapy

Unfortunately, except for small bowel cultures which are impractical and expensive there is no other reliable test to diagnose SIBO [16]. The lactose hydrogen breath test (LHBT) may be alternatively used as a surrogate marker for SIBO. Administration of a test dose of lactulose in SIBO patients is associated with an early rise in breath hydrogen levels secondary to abnormal consumption of lactulose by excessive small intestinal bacteria followed by the normal later peak which is due to metabolism of lactulose in the colon.

There is a high degree of variability in the literature regarding the proportion of healthy subjects and IBS patients with abnormal LHBT. Pimentel *et al.* reported positive LHBT in up to 84% of IBS patients [17] compared with 20% in healthy controls. In contrast, Sharara *et al.* [13] and Parisi *et al.* [18], using lactulose breath test and glucose breath test respectively, found no abnormality in IBS patients. Consistent with a study by Walters *et al.* [19], Bratten *et al.* [20] reported a positive LHBT in 85% of healthy subjects compared to 74% of IBS patients.

The lactulose hydrogen breath test has been shown to have a poor sensitivity (17%) and specificity (70%) to diagnose SIBO [21], with several potential confounding factors capable of inducing false positive results such as fast bowel transit.

Despite several technical limitations with LHBT to diagnose SIBO, it is possible that alteration of gut flora is responsible for IBS symptoms at least in some patients.

Several studies have shown quantitative and qualitative differences in intestinal bacterial flora of IBS patients compared to healthy controls [22, 23]. Abnormal enteric bacterial flora may lead to over-production of gas and changes in fatty acid production which results in deconjugation of bile salts and disruption of electrolyte and water transport. The latter might affect bowel motility with clinically significant symptoms. These findings have been the scientific basis for the use of probiotics in IBS [24, 25]. However, the majority of enteric flora are still unculturable with current

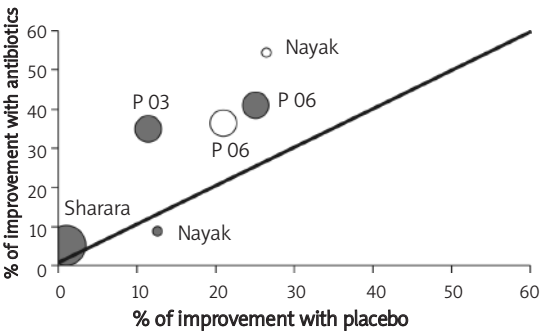

Figure 4. L'Abbe plot for short-term (dark symbols) and long-term (hollow symbols) improvement of IBS-type symptoms

means and precise microbiological mapping of the gut in IBS patients is far from being achieved.

The L'Abbe plot (Figure 4) is suggestive of publication bias with lack of negative small RCTs (i.e. studies below the line of equality). Only Nayak *et al*. reported a superior effect of placebo in the first part of their study; however, in the second phase of the trial metronidazole was superior to placebo. A definite conclusion regarding the presence of publication bias is elusive to achieve as asymmetry of the plots may occur for various other reasons [26]. Publication bias in functional disorders has been reported previously [27]. Therefore, our pooled relative risk might be an overestimate of the true effect.

Two studies do not report dichotomous results and rather reported improvement in clinical symptoms [11, 12]; however, if the hypothesis behind these studies was "bacterial overgrowth as the cause of IBS", a conventional comparison of responders versus non-responders would have been favoured.

Given the lack of a precise scientific explanation for the role of gut flora in pathophysiology of IBS, use of antibiotics on a regular basis in IBS patients is not justified.

SIBO is not a true unifactorial disease; rather, it is a consequence of an underlying dysmotility of the bowels. The underlying cause of SIBO is usually not reversible and recurrence may occur after discontinuation of antibiotics [28]. Thus, studies with a longer period of follow-up are needed. Further studies integrating reliable diagnostic approaches for SIBO are needed. Emergence of the double balloon study may pave the way to evaluate presence of SIBO in IBS patients with jejunal aspirates, which is a more reliable test for diagnosis of SIBO [16].

Despite a safe profile of antibiotics in the RCTs included in this meta-analysis, it should also be kept in mind that widespread use of antibiotics may result in emergence of opportunistic bacterial infections and bacterial resistance. Brigidi *et al.* have reported isolation of rifaximin-resistant bacteria in ulcerative colitis patients treated with 1800 mg/day for a total period of 30 days [29].

In conclusion, it is possible that antibiotics have some beneficial effects in IBS patients, especially with bloating as the predominant symptom. However, in the absence of a proven pathophysiological explanation for the role of antibiotics in IBS, routine use of antibiotics in IBS and IBS-type symptoms cannot be recommended. Larger studies with standardized outcomes and reliable testing for SIBO (e.g. glucose hydrogen testing) are required.

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