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Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth

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SUMMARY

Background
Small intestinal bacterial overgrowth (SIBO) is an under-recognised diagnosis with important clinical implications when untreated. However, the optimal treatment regimen remains unclear.

Aim
To perform a systematic review and meta-analysis comparing the clinical effectiveness of antibiotic therapies in the treatment of symptomatic patients with documented SIBO.

Methods
Four databases were searched to identify clinical trials comparing effectiveness of: (i) different antibiotics, (ii) different doses of the same antibiotic and (iii) antibiotics compared with placebo. Data were independently extracted according to predetermined inclusion and exclusion criteria. Study quality was independently assessed. The primary outcome was normalisation of post-treatment breath testing. The secondary outcome was post-treatment clinical response.

Results
Of 1356 articles identified, 10 met inclusion criteria. Rifaximin was the most commonly studied antibiotic (eight studies) with overall breath test normalisation rate of 49.5% (95% confidence interval, CI 44.0–55.1) (44.0%–55.1%) then (46.7%–55.5%), then (4.6%–17.8%). Antibiotic efficacy varied by antibiotic regimen and dose. Antibiotics were more effective than placebo, with a combined breath test normalisation rate of 51.1% (95% CI 46.7–55.5) for antibiotics compared with 9.8% (95% CI 4.6–17.8) for placebo. Meta-analysis of four studies favoured antibiotics over placebo for breath test normalisation with an odds ratio of 2.55 (95% CI 1.29–5.04). Clinical response was heterogeneously evaluated among six studies, but tended to correlate with breath test normalisation.

Conclusions
Antibiotics appear to be more effective than placebo for breath test normalisation in patients with symptoms attributable to SIBO, and breath test normalisation may correlate with clinical response. Studies were limited by modest quality, small sample size and heterogeneous design. Additional higher quality clinical trials of SIBO therapy are warranted.

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INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is an under-recognised diagnosis with varied and often protean manifestations.[1–3] Because the clinical presentation of SIBO can range from mild, nonspecific symptoms (such as abdominal pain, bloating and flatulence) to less common but severe manifestations (such as malabsorption, weight loss and hypoalbuminaemia), a delay in diagnosis is not uncommon.[2, 4, 5] Although epidemiological data describing SIBO are limited, there appears to be increased prevalence of SIBO in patients with risk factors such as hypochlorhydria, gastroparesis or other motility disorders, anatomical abnormalities (such as small bowel diverticulosis), post-surgical state (such as ileocecal resection), small bowel mucosal disease, metabolic diseases (such as diabetes) and other chronic diseases (such as end-stage renal disease, cirrhosis, chronic pancreatitis).[2, 6, 7] Prevalence in the elderly may be as high as 15%,[3] and even higher among elderly patients with additional risk factors.[3, 8–10]

Treatment of SIBO typically includes antibiotics and, when possible, addressing underlying predisposing conditions.[11] Although a diagnosis of SIBO is often entertained and empirically treated among at-risk patients with gastrointestinal symptoms, comparison trials of antibiotic regimens remain disparate, and the optimal antibiotic regimen is not known. To address this important knowledge gap, we performed a systematic review to compare the effectiveness of antibiotics for achieving breath test normalisation among symptomatic patients with documented SIBO. When feasible, we performed meta-analyses to further characterise the role of antibiotics in SIBO treatment.

MATERIALS AND METHODS

Systematic review and study selection

We performed a systematic review using four primary databases to identify clinical trials of antibiotic therapy among symptomatic patients with documented SIBO. No restrictions were applied to language or publication date. Databases searched were as follows: (i) PubMed (original search date July 5, 2012; updated search July 3, 2013); (ii) Web of Science (original search date July 5, 2012; updated search July 3, 2013); (iii) Embase (original search date July 10, 2012; updated search July 3, 2013); and (iv) Cochrane (search date July 3, 2013). Search strings were as follows. For PubMed: '*bacterial overgrowth*' *OR* '*small intestinal bacterial overgrowth*' OR '*SIBO*' *AND Humans[Mesh] AND (Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Randomized Controlled Trial[ptyp])*. For Web of Science: *clinical trial AND* ('*bacterial overgrowth*' *OR* '*small intestinal bacterial overgrowth*' *OR* '*SIBO*'). For Embase: '*bacterial overgrowth*' *OR sibo:ab,ti AND* ('*clinical trial*'/*exp OR* '*controlled study*'/de OR '*randomization*'/*de OR randomized:ab,ti*) *AND* (*[humans]/lim OR patient*). For Cochrane: '*small intestinal bacterial overgrowth*'. We hand-searched reference lists from included studies to identify additional relevant studies for inclusion. Embase and Web of Science were used to search published abstracts. Because trials of SIBO therapy would likely be reported within several different types of professional society meetings (i.e. gastroenterology, infectious disease, general internal medicine, family medicine), we did not search the proceedings of any specific professional society meetings. See Figure 1 for a summary of the literature search and study selection.

Studies were eligible for inclusion if they reported prospective clinical trials of antibiotic therapy for documented SIBO among human subjects. We included trials comparing two or more antibiotics, trials comparing two or more dosing strategies for the same antibiotic, or trials comparing one or more antibiotics with placebo. Retrospective studies, case reports, and case series were excluded due to the high risk of publication bias. Although we did not plan to exclude studies based on language, our literature search did not produce any non-English studies meeting inclusion criteria. Table 1 details inclusion criteria, and Figure 1 describes reasons for study exclusion.

Data abstraction

The primary outcome assessed was normalisation of either lactulose or glucose breath testing. Additional data abstracted included country of origin, study design, dates of enrolment, types of patients enrolled, antibiotic and dietary restrictions, method for diagnosing SIBO, definition of breath test normalisation, antibiotic regimen used, number enrolled in each treatment arm, number with response/cure in each treatment arm and adverse events. When both intention-to-treat and per-protocol data were reported, we used intention-to-treat data. For trials with more than two treatment arms, each of the treatment arms was considered separately for purposes of pooled data analysis and possible inclusion in meta-analysis. Two authors (JLS and LWD) independently extracted data using a set of inclusion and exclusion criteria and pre-specified definitions. The two authors independently abstracted and entered data into

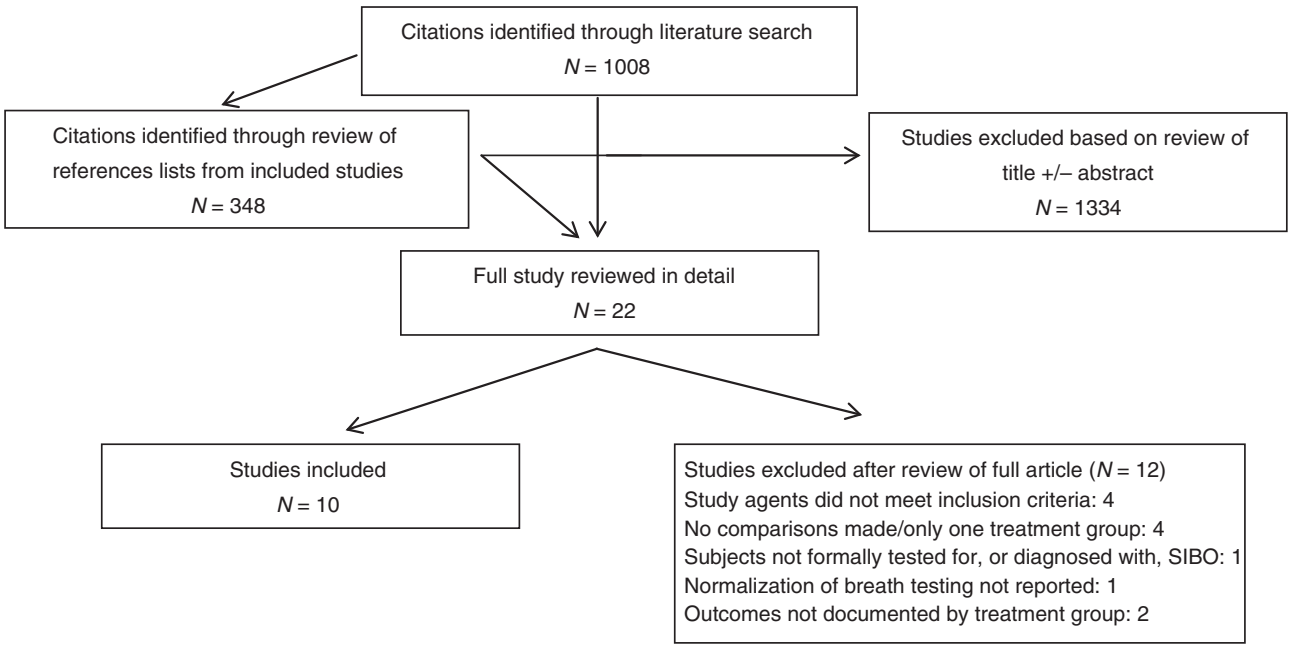

Figure 1 | Results of literature search.

Table 1 | Study inclusion criteria

Inclusion criteria
Prospective clinical trial comparing two or more antibiotics, two or more doses of the same antibiotic or comparing an antibiotic vs. placebo, for the treatment of human subjects with documented SIBO
Primary study goal of evaluating medical therapy among symptomatic patients with SIBO
SIBO formally diagnosed with lactulose, glucose, sucrose, or xylose hydrogen or methane breath test, and/or quantitative small bowel culture
Study agents and dosing schedule clearly defined
'Cure' or 'treatment response' defined as normalisation of repeat hydrogen breath testing
Treatment outcomes clearly documented for each study group

separate spreadsheets. The data were subsequently compared. Disagreement between the two authors was resolved by consensus. If consensus could not be reached, a third party (MS) served as arbiter.

Outcomes

The primary outcome was normalisation of repeat breath testing, confirming eradication of SIBO. This was chosen as the most objective outcome. We also sought to assess clinical response as a secondary outcome. Due to significant heterogeneity in methods for measuring and reporting symptoms pre- and post-treatment, meta-analysis of symptoms was not possible, but we report on clinical response descriptively, based on the methods used to measure clinical response in each included article.

Quality assessment

We used guidance from the Cochrane Handbook for Systematic Reviews of Interventions[12] to assess quality in the following areas: sequence generation, allocation concealment, blinding (of participants, personnel and outcome assessment), incomplete outcome data, selective outcome reporting and other sources of bias. Two authors (JLS, LWD) independently assessed study quality across the above categories. Independently abstracted quality scores were entered by the two authors into separate spreadsheets and then compared. Differences in scoring were resolved via consensus. If consensus could not be reached, a third party (MS) served as arbiter.

Statistical analysis

The rate of breath test normalisation was determined for each study. Because numerous different antibiotic comparisons were studied, we calculated the pooled rate of breath test normalisation for different antibiotics. For rifaximin, this was calculated across varying doses: low dose (600–800 mg/day), medium dose (1200 mg/day) and high dose (1600–1650 mg/day). Data from individual studies were pooled and weighted by sample size.

The mean rate of breath test normalisation was calculated along with the 95% confidence interval (CI) using the CI calculator in Stata.

When feasible, meta-analysis was performed to compare breath test normalisation among different treatment regimens. A random-effects model estimated the weighted average of the breath test normalisation rate ratio between treatment interventions.[13] Relative risk ratios for normalisation of breath tests with 95% CIs were calculated for each analysis, and a forest plot was generated to graphically represent the available studies. Due to the small number of studies that were appropriate for meta-analysis, sensitivity analyses were not possible. A statistically significant result was observed with a 95% CI not crossing 1.0 and a P value <0.05. Heterogeneity was calculated using Mantel–Haenszel chi-squared test with a $P < 0.10$ representing significant heterogeneity. Because it was only possible to meta-analyse four relatively small studies, we did not assess for publication bias, because the small sample size made such analysis unreliable. All statistical analyses were calculated using STATA 11.0 (Stata Corp, College Station, TX, USA).

RESULTS

Search results

Primary literature search and review of citations from included articles produced 1356 articles. 1334 of these were excluded based on review of the title and/or abstract. Twenty-two full articles were reviewed in detail. Ten of these met criteria for inclusion, and 12 were excluded for various reasons (Figure 1).

Characteristics of included studies

The 10 included studies are summarised in Tables 2 and 3.[6, 14–21] Seven of the studies were performed in Italy and three were performed in the United States. Most studies were open-label, randomised trials. Five studies included adults with symptoms of SIBO, two included patients with Crohn's disease, one included patients with formally diagnosed irritable bowel syndrome, one included subjects with coeliac disease, and one included children with chronic abdominal pain. The mean sample size per study was 63 subjects (range 14–142), and mean number per treatment arm was 30 (range 7–71). Rifaximin was the most commonly studied antibiotic (8 of 10 studies). Only two antibiotics were evaluated in more than one study. Pre-enrolment restrictions varied. Testing for eradication was performed between 3 and 30 days after completing the treatment course.

Breath test normalisation

The pooled rate of breath test normalisation varied widely across different antibiotics and doses (Table 4). Rifaximin monotherapy was evaluated in eight studies with pooled rate of breath test normalisation ranging from 21.7% (95% CI 12.1–34.2) at low doses to 46.1% (95% CI 35.4–57.0) at high doses to 60.8% (95% CI 53.2–68.1) at medium doses. For all trials of rifaximin monotherapy combined, the aggregate breath test normalisation rate was 49.5% (95% CI 44.0–55.1). Rifaximin combined with partially hydrolysed guar gum was used in one study with a breath test normalisation rate of 85% (95% CI 70.2–94.3). Metronidazole was used in two studies, with a combined breath test normalisation rate of 51.2% (95% CI 40.1–62.1). Ciprofloxacin had the highest rate of breath test normalisation (100%, 95% CI 76.8–100.0), but this was based on a single study with only 14 subjects in each treatment arm. For all antibiotic regimens combined, breath test normalisation occurred in 51.1% (95% CI 46.7–5.5). Conversely, only 9.8% (95% CI 4.6–17.8) of placebo-treated subjects among four studies had breath test normalisation.

Clinical response

Two studies objectively documented clinical response depending on whether subjects had breath test normalisation. Furnari *et al.* reported 'clinical improvement' as a global symptom score reduction of ≥50%.[15] For the rifaximin arm, 87% of subjects with breath test normalisation achieved clinical improvement vs. only 7% with persistently abnormal breath tests. For the rifaximin plus partially hydrolysed guar gum arm, these proportions were 91% and 17% respectively. Pimentel *et al.* reported 'true clinical response' as a ≥50% reduction in overall composite score of irritable bowel syndrome symptoms (including abdominal pain, diarrhoea and constipation).[6] 46% receiving neomycin had a true clinical response vs. 15% receiving placebo. Subjects receiving neomycin with normalisation of lactose breath testing had significantly greater reduction in their composite symptom score (61.7% reduction) compared with subjects receiving neomycin whose breath tests did not normalise (34.4% reduction) and subjects receiving placebo (4.1% reduction).

Four studies reported on symptomatic response, but did not stratify outcomes by breath test normalisation. Di Stefano *et al.* reported greater reduction in a cumulative symptom score among subjects treated with rifaximin compared with chlortetracycline (mean score 6.3 pre-treatment to 5.2 post-treatment for rifaximin vs. 6.6

Table 2 | Characteristics of included studies

Study	Country	Study design	Study dates	Patient population*	Trial agents	Method of SIBO diagnosis	Test of SIBO eradication	Days of antibiotic restriction before testing	Dietary restrictions†	Other restrictions
Collins (2011)	United States	DB, RCT	Not reported	Children with chronic abdominal pain	Rifaximin vs. placebo	LBT	LBT normal 14 days after treatment	60	Light meal the night before	No probiotics for 60 days
Chang (2011)	United States	DB, RCT	2006–2008	Coeliac patients with abdominal symptoms	Rifaximin vs. placebo	LBT	LBT normal 4 days after treatment	30	Multiple food exclusions the day before	None
Furnari (2010)	Italy	OL, RT	2007–2010	Adults with SIBO symptoms	Rifaximin vs. Rifaximin plus PHGG	GBT	GBT normal 30 days after treatment	10	Boiled rice, meat and water the night before	No probiotics or proton pump inhibitors for 10 days
Lauritano (2009)	Italy	OL, RT	2005–2007	Adults with SIBO symptoms	Rifaximin vs. metronidazole	GBT	GBT normal 30 days after treatment	90	Carbohydrate restricted the night before	No laxatives for 30 days
Scarpellini (2007)	Italy	OL, RT	2004–2006	Adults with SIBO symptoms	Rifaximin (compared multiple doses)	GBT	GBT normal 30 days after treatment	90	Carbohydrate restricted the night before	No laxatives for 30 days
Lauritano (2005)	Italy	OL, RT	2003–2004	Adults with SIBO symptoms	Rifaximin (compared multiple doses)	GBT	GBT normal 30 days after treatment	30	Carbohydrate restricted the night before	No laxatives for 30 days
Castiglione (2003)	Italy	OL, RT	2000–2002	Adults with Crohn's disease	Metronidazole vs. ciprofloxacin	LBT followed by GBT	GBT normal 7 days after treatment	30	No starch for 48 h	None
Pimentel (2003)	United States	DB, RCT	Not reported	Adults meeting Rome I criteria for IBS	Neomycin vs. placebo	LBT	LBT normal 7 days after treatment	90	No legumes or heavy foods the night before	'All use prohibited'
Biancone (2000)	Italy	Blinded‡, RT	Not reported	Adults with Crohn's disease	Rifaximin vs. placebo	GBT	GBT normal 14 days after treatment	Not reported	No specific restrictions	None
Di Stefano (2000)	Italy	DB, RT	Not reported	Adults with SIBO symptoms	Rifaximin vs. chlortetracycline	GBT	GBT normal 3 days after treatment	30	Rice, meat and olive oil the evening before	None

DB, double-blinded; GBT, glucose breath test; IBS, irritable bowel syndrome; LBT, lactulose breath test; OL, open-label; PHGG, partially hydrolysed guar gum; RCT, randomised controlled trial; RT, randomised trial; SIBO, small intestinal bacterial overgrowth.

* These data are meant to be descriptive and do not represent analytical subgroups.

† Unless otherwise stated, subjects were NPO for 12 h before testing.

‡ Unclear whether single- or double-blinded.

to 6.4 for chlortetracycline).[21] Castiglione *et al.* found no differences in bloating, stool quality or abdominal pain comparing metronidazole with ciprofloxacin (composite score not reported).[19] The Chang and Collins studies reported no differences in symptoms for subjects treated with rifaximin vs. placebo, but objective data were not reported in either study.[14, 22]

Four of the studies[16–18, 20] reported no data regarding symptoms.

Meta-analysis

Two meta-analyses were possible. The first included four studies[6, 14, 20, 22] comparing any antibiotic therapy with placebo (Figure 2). Although these studies included heterogeneous populations, there was no evidence of statistical heterogeneity ($P = 0.32$ for heterogeneity). Treatment of SIBO with any antibiotic was associated with higher rate of breath test normalisation compared with placebo (effectiveness ratio 2.55, 95% CI 1.29–5.04, $P = 0.03$).

The second meta-analysis included three studies[14, 20, 22] comparing rifaximin with placebo (Figure 3). Although these studies included heterogeneous populations, there was no evidence of statistical heterogeneity ($P = 0.41$ for heterogeneity). Treatment with rifaximin was associated with a higher rate of breath test normalisation compared with placebo, although this was not statistically significant (effectiveness ratio 1.97, 95% CI 0.93–4.17, $P = 0.08$).

Table 3 | Treatment arms and outcomes by study

Study	Treatment arm 1*	Subjects in treatment arm 1, *n*	Cures in treatment arm 1, *n* (%)	Treatment arm 2*	Subjects in treatment arm 2, *n*	Cures in treatment arm 2, *n* (%)	Statistical significance
Collins (2011)	Rifaximin 1650 mg/day ×10 days	49	9 (18.4)	Placebo three times daily ×10 days	26	3 (11.5)	NS
Chang (2011)	Rifaximin 1200 mg/day ×10 days	11	2 (18.2)†	Placebo three times daily ×10 days	16	3 (18.8)†	NS
Furnari (2010)	Rifaximin 1200 mg/day ×10 days	37	23 (62.2)	Rifaximin 1200 mg/day plus PHGG 5 g daily ×10 days	40	34 (85.0)	$P < 0.05$
Lauritano (2009)	Rifaximin 1200 mg/day ×10 days	71	45 (63.4)	Metronidazole 250 mg three times daily ×10 days	71	31 (43.7)	$P < 0.05$
Scarpellini (2007)	Rifaximin 1600 mg/day ×7 days	40	32 (80.0)	Rifaximin 1200 mg/day ×7 days	40	23 (57.5)	$P < 0.05$
Lauritano (2005)	Rifaximin 600 mg/day ×7 days	30	5 (16.7)	Rifaximin 800 mg/day ×7 days	30	8 (26.7)	$P < 0.05$ for arm 3‡ compared with arms 1 and 2
Castiglione (2003)	Metronidazole 250 mg three times daily ×10 days	15	13 (86.7)	Ciprofloxacin 500 mg twice daily ×10 days	14	14 (100.0)	NS
Pimentel (2003)	Neomycin 500 mg twice daily ×10 days	41	8 (19.5)	Placebo twice daily ×10 days	43	1 (2.3)	Not reported
Biancone (2000)	Rifaximin 1200 mg/day ×7 days	7	7 (100.0)	Placebo three times daily ×7 days	7	2 (28.6)	$P < 0.05$
Di Stefano (2000)	Rifaximin 1200 mg/day ×7 days	10	7 (70.0)	Chlortetracycline 333 mg three times daily ×7 days	11	3 (27.3)	$P < 0.05$

NS, not significant; PHGG, partially hydrolysed guar gum.

* For rifaximin, dose is total daily dose. Unless otherwise stated, these were divided into three times daily dosing.

† Number of cures for each treatment arm not extractable from published manuscript; data obtained through communication with study authors.

‡ Study had a third treatment arm, which included 30 subjects treated with Rifaximin 1200 mg/day for 7 days. There were 18 cures (60%).

Quality assessment

Quality of reporting across the studies varied. No studies showed evidence of selective outcome reporting, and two studies had incomplete outcome data. The protocol for sequence generation of antibiotic and/or placebo was high quality in six studies, but reporting was inadequate to characterise sequence generation in the other four studies. Seven studies had high-quality allocation concealment, while three studies did not provide enough information to classify allocation concealment. Reporting of blinding was adequate in 9 of 10 studies; however, only four studies had high-quality blinding of participant, personnel and outcome. Six studies reported funding that did not indicate any apparent conflict of interest. Two studies did not report a funding source, while two studies reported pharmaceutical company funding. See Table S1 for more details.

DISCUSSION

Given the prevalence of SIBO and its potential for significant consequences when left untreated, we found a surprising lack of depth in the literature describing antibiotic therapy for SIBO. Our extensive literature search produced only 10 studies describing antibiotic trials for SIBO meeting inclusion criteria. The majority of studies were of modest size, and most were open-label randomised trials. Only two antibiotics (metronidazole

Table 4 | Pooled breath test normalisation rates

Treatment	Number of studies	Total number of subjects	Number with breath test normalisation	Per cent with breath test normalisation	95% confidence interval*
Rifaximin 1600 or 1650 mg/day	2	89	41	46.1	35.4–57.0
Rifaximin 1200 mg/day	6	176	107	60.8	53.2–68.1
Rifaximin 600 or 800 mg/day	1	60	13	21.7	12.1–34.2
Rifaximin monotherapy (all doses combined)	8	325	161	49.5	44.0–55.1
Rifaximin plus PHGG	1	40	34	85.0	70.2–94.3
Metronidazole	2	86	44	51.2	40.1–62.1
Neomycin	1	41	8	19.5	8.8–34.9
Ciprofloxacin	1	14	14	100.0	76.8–100.0
Chlortetracycline	1	11	3	27.3	6.0–61.0
All antibiotics	10	517	264	51.1	46.7–55.5
Placebo	4	92	9	9.8	4.6–17.8

PHGG, partially hydrolysed guar gum.

* Calculated using the confidence interval function of Stata.

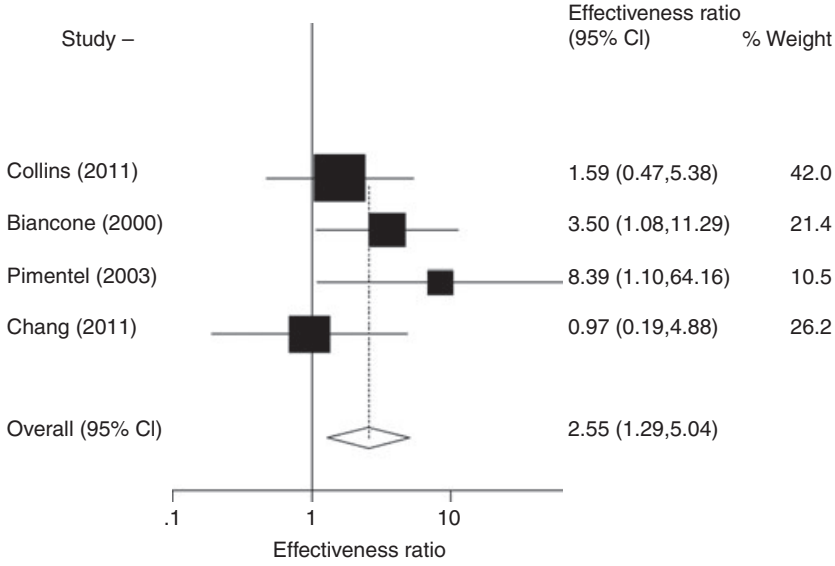

Figure 2 | Meta-analysis of any antibiotic vs. placebo.

and rifaximin) were evaluated in more than one study. Only four studies compared antibiotics with placebo, and meta-analysis of these studies suggested modest benefit of antibiotic over placebo. Our findings call attention to several important issues and considerations for SIBO therapy and research moving forward.

In the meta-analyses, we were unable to reject the null hypothesis of no statistical heterogeneity, likely due to the small number of studies meta-analysed. For the 10 studies included in our overall review, though, there was evident heterogeneity in study design, including populations studied, pre-study restrictions, treatment regimens used, type and timing of breath testing, and assessment of clinical response (Table 2). This limits our ability to draw firm conclusions regarding choice of antibiotics for breath test normalisation among patients with SIBO.

Measurement of symptoms pre- and post-treatment was even more heterogeneous. Only two studies[6, 15] reported symptom data using objective, composite clinical scores. Unfortunately, the remaining eight studies were much more limited, with four studies reporting on clinical response in a limited fashion,[14, 19, 21, 22] and the other four reporting no data regarding symptoms and clinical response.[16–18, 20] As SIBO therapy is most frequently driven by a desire to reduce or eliminate bothersome symptoms, this is an important gap in the literature that should be addressed. Specifically, additional large, randomised, double-blind trials assessing both breath test normalisation and objectively measured symptomatic response are needed.

Because case series and observational studies carry significant risk of publication bias, we chose *a priori* to

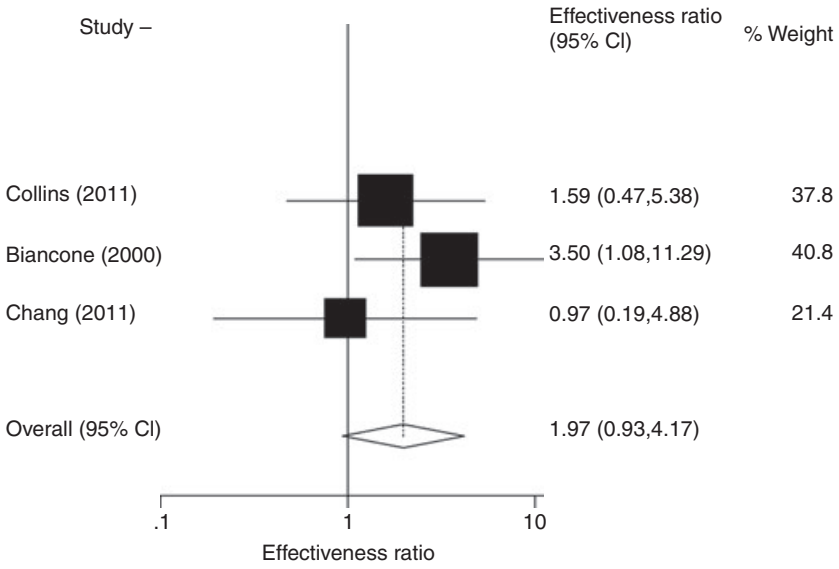

Figure 3 | Meta-analysis of rifaximin vs. placebo.

include only clinical trials comparing placebo and/or antibiotics. Given the limited nature of our meta-analysis, we chose to calculate pooled rates of breath test normalisation for the various treatment regimens, including varying doses of rifaximin (Table 4). The purpose of this analysis was to provide summative data that would be more clinically useful. Rifaximin was the most commonly studied antibiotic, with 8 of 10 studies evaluating monotherapy at varying doses. The overall breath test normalisation rate for rifaximin monotherapy was only 49.5% (95% CI 44.0–55.1), but this ranged widely from 16.7% to 100%. This wide range may be attributable to variability in study populations, dosing strategies and timing of post-treatment breath testing. In meta-analysis (Figure 3), rifaximin had an effectiveness ratio of 1.97 compared with placebo, but this was not statistically significant (95% CI 0.93–4.17, $P = 0.08$). The lack of statistical significance likely relates to relatively small numbers of subjects (67 subjects received rifaximin and 49 received placebo among all three studies combined), and it is possible that a true benefit for rifaximin exists compared with placebo.

Other antibiotics were notably less studied, with metronidazole being most common after rifaximin, and still limited to only two studies. As rifaximin is costly and may be unavailable to many patients, more thorough investigation of alternate antibiotic choices is warranted, ideally double-blind studies comparing other antibiotics with rifaximin. Such data would be useful not only for primary treatment of SIBO but also to inform therapeutic choices for patients with recurrent or refractory SIBO, which are not uncommon clinical entities.[10, 23]

Numerically, the most effective antibiotic was ciprofloxacin, with a 100% breath test normalisation rate, but the single study included only 14 subjects in each arm.[19] Aside from this small trial, the most effective treatment regimen was rifaximin plus partially hydrolysed guar gum, which was associated with an 85% breath test normalisation rate.[15] Partially hydrolysed guar gum is a prebiotic agent that favours growth of *Bifidobacteria* and *Lactobacillus* spp., among others.[24] Treatment with antibiotics alone does not fully address the microbial dysbiosis associated with SIBO, as antibiotics do not restore normal flora.[15] Accordingly, the addition of pre- or probiotics is an attractive option.[25] Probiotics are postulated to enhance gut barrier function, decrease inflammatory response, stabilise gut flora and potentially modulate visceral hypersensitivity.[26] Their use has been best described among patients with irritable bowel syndrome and *Clostridium difficile* infection[27–30] and our understanding of these therapies in SIBO remains limited. Prebiotics, in contrast, alter gut microbiota indirectly by favouring growth of certain bacterial species via provision of metabolites. The therapeutic profile of prebiotics is less well defined and available data are generally of poor quality.[31] As noted above, the Furnari[15] study was the only study meeting inclusion criteria that included a prebiotic, and none of the studies meeting inclusion criteria included a probiotic arm. In our overall search of the literature, only one other fully reviewed article included a probiotic arm.[32] In this small study (which did not meet inclusion criteria), the administration of oral *Lactobacillus* spp. did not reduce symptoms or result in breath test normalisation among patients with SIBO.[32] The role of microbiome-related therapy for SIBO is intuitive. As techniques to study the human microbiome advance, this will become an increasingly important area for further attention and research.

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We chose to assess breath test normalisation as our primary outcome of interest due to its ubiquity in SIBO trials and the aforementioned lack of standardisation in symptom reporting. Proximal intestinal aspirates were previously accepted as the gold standard for diagnosing SIBO, but methodological considerations (such as obtaining a representative sample, culturing fastidious bacteria, and differentiating culprit strains from contamination or non-pathogenic strains) limits the utility of this test, particularly if repeat testing after treatment is desired.[3] Indirect tests for SIBO, such as breath test analysis, are therefore appealing.[3] The sensitivity and specificity of breath testing varies, but glucose breath testing (sensitivity 63%, specificity 82%, diagnostic accuracy 72%) is thought to be more accurate than lactulose breath testing (sensitivity 52%, specificity 86%, diagnostic accuracy 55%).[2]

The transition from an abnormal breath test to a normal breath test provides biological evidence of a treatment's effectiveness in eradicating bacteria in the small intestine, which is necessary to 'cure' SIBO. The two studies documenting clinical response by breath test normalisation[6, 15] clearly demonstrate that breath test normalisation is highly associated with reduction in symptoms attributable to SIBO. This is further supported by the four studies reporting limited clinical response data. The one study identifying differences in breath test normalisation between treatment arms[21] found analogous differences in clinical response, whereas the three studies without differences in breath test normalisation between treatment arms[14, 19, 22] failed to find differences in clinical response. These data suggest that breath test normalisation may correlate with symptomatic response. Repeat breath testing among patients who have been treated for SIBO, yet remain symptomatic, may, therefore, have utility in clinical practice, as it may help clarify whether persistent SIBO is the source of ongoing symptoms, or if other aetiologies, such as irritable bowel syndrome, should be considered. There are strong data supporting a robust association between SIBO and irritable bowel syndrome, with two meta-analyses identifying a 3.5- to 9.6-fold increased odds of SIBO in patients with irritable bowel syndrome.[33, 34] That rifaximin has been shown to be an effective therapy for irritable bowel syndrome patients without constipation further supports the role of SIBO in irritable bowel syndrome.[35]

In summary, we identified 10 studies comparing antibiotic therapies for SIBO. Antibiotic therapy appears to be superior to placebo for the eradication of SIBO, but the small number of heterogeneously designed studies prevented more detailed meta-analyses of different treatment regimens. Future studies of SIBO should address the shortcomings of these studies. Trials involving larger patient populations, comparing a greater diversity of antibiotics with one another and with placebo, are needed. The use of objective measures of clinical response among patients being treated for SIBO is critical, as is longer term follow-up assessing durability of response and risk of relapse among patients successfully treated.

AUTHORSHIP

Guarantor of the article: Dr. J. L. Sewell.

Author contributions: Drs. Sewell, Day and Somsouk had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Sewell, Day and Somsouk contributed to the study concept and design. Sewell contributed to the acquisition of data. Sewell, Day, Somsouk and Shah performed the analysis and interpretation of data. Sewell and Shah drafted the manuscript. Day, Somsouk and Sewell performed the critical revision of manuscript for important intellectual content. Sewell, Day and Somsouk performed the statistical analysis. Sewell, Day and Somsouk contributed to the study supervision. We thank Gloria Won, MLIS, for her assistant with the literature search. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Assessment of quality.

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