

# Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth

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## Publication data

Submitted 8 August 2016  
First decision 2 September 2016  
Resubmitted 21 November 2016  
Resubmitted 11 December 2016  
Accepted 12 December 2016  
EV Pub Online 12 January 2017

*As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Roy Pounder, and it was accepted for publication after full peer-review.*

## SUMMARY

### Background

Small intestinal bacterial overgrowth (SIBO) is a heterogeneous syndrome, characterised by an increased number and/or abnormal type of bacteria in the small bowel. Over the past decades, rifaximin has gained popularity for this indication despite its use is not evidence based.

### Aim

To perform a systematic review and meta-analysis to summarise evidence about the efficacy and safety of rifaximin to eradicate SIBO in adult patients.

### Methods

MEDLINE, EMBASE, CCRCT, Scopus and Web of Science were searched from inception to March 16, 2015 for RCTs and observational studies. Furthermore, abstract books of major European, American and Asian gastroenterological meetings were also examined.

### Results

Thirty-two studies involving 1331 patients were included. The overall eradication rate according to intention-to-treat analysis was 70.8% (95% CI: 61.4–78.2;  $I^2 = 89.4\%$ ) and to per protocol analysis 72.9% (95% CI: 65.5–79.8;  $I^2 = 87.5\%$ ). Meta-regression identified three covariates (drug dose, study design and co-therapy) independently associated with an increased eradication rate. The overall rate of adverse events was 4.6% (95% CI: 2.3–7.5;  $I^2 = 63.6\%$ ). In the subset of studies ( $n = 10$ ) allowing the analysis, improvement or resolution of symptoms in patients with eradicated SIBO was found to be 67.7% (95% CI: 44.7–86.9;  $I^2 = 91.3\%$ ).

### Conclusions

Rifaximin treatment seems to be effective and safe for the treatment of SIBO. However, the quality of the available studies is generally poor. Well-designed RCTs are needed to substantiate these findings and to establish the optimal regimen.

*Aliment Pharmacol Ther* 2017; 45: 604–616

## INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is a heterogeneous syndrome characterised by an increased number and/or abnormal type of bacteria in the small bowel, and it is a well-recognised cause of maldigestion and malabsorption.<sup>1, 2</sup>

The recent discovery of an association between SIBO and functional gut symptoms, albeit controversial, has renewed interest in this mimicry. SIBO represents indeed an umbrella term, under which some different functional (e.g. irritable bowel syndrome, chronic constipation, diarrhoea) or organic (e.g. inflammatory bowel disease, coeliac disease, diverticular disease, etc.) conditions can be included, as – in each of them – bacterial proliferation (and consequent inflammation) may, at least in part, trigger similar abdominal symptoms.<sup>1</sup>

The overall, true prevalence of SIBO – which is usually under-diagnosed – is unknown.<sup>2, 3</sup> Indeed, patients may not seek healthcare and SIBO may not be properly diagnosed by medical investigations. In addition, the diagnostic yield depends on the methodology adopted, so that results from different studies are difficult to compare.<sup>4, 5</sup>

The mainstay of the SIBO treatment is based on the use of antimicrobial agents, whose aims should not be to eradicate the entire bacterial flora but rather to modify the intestinal microecology in order to get symptoms relief.<sup>1</sup> Ideally, the choice of antimicrobials should reflect *in vitro* susceptibility testing, but this is usually impractical because intestinal bacterial cultures need invasive methodology to collect samples under sterile conditions.<sup>6</sup> Therefore, hydrogen breath test (HBT) is widely used as non-invasive means to diagnose SIBO. As consequence, in clinical practice antibiotic treatment, which should cover both aerobic and anaerobic bacteria, remains primarily empiric.<sup>4–6</sup>

Several antibiotic regimens proved to be effective over the past 50 years, with treatment success ranging from 27% to 100%.<sup>7</sup> Till the end of 90s, only systemic antimicrobials were used, whose adverse events (AEs) and detrimental effects on gut microbiota are today well known.<sup>8</sup> Poorly absorbed antibiotics, unlike systemic ones, allow localised targeting of enteric pathogens and are associated with minimal risk of systemic toxicity or AEs. The restricted use of drugs only for enteric-infections should also reduce the development of widespread resistance, especially of enterobacteria, a major limitation of current antibiotics.<sup>8</sup>

Rifaximin is a product of synthesis experiments designed to modify the parent compound, rifamycin, in

order to achieve low gastrointestinal absorption while retaining good antibacterial activity.<sup>9–11</sup> Both experimental and clinical pharmacology have clearly shown that this compound is a poorly absorbed antibiotic with a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative microorganism, both aerobes and anaerobes.<sup>10–13</sup>

Rifaximin fulfils all the characteristics set by DuPont and Ericsson<sup>14</sup> for the ideal antimicrobial that should be used for the treatment of gastrointestinal infections (including dysbiosis and SIBO). As a consequence, over the past decades, rifaximin has been largely used to treat SIBO<sup>1, 7</sup> even if there is currently a lack of a critical summary of evidence. To bridge this gap, a systematic review and meta-analysis of randomised and nonrandomised studies was performed to evaluate the clinical effectiveness of and safety rifaximin to eradicate SIBO in adult patients.

## METHODS

### Search strategy and study selection

This meta-analysis was developed according to the PRISMA<sup>15</sup> and to the MOOSE<sup>16</sup> statement guidelines. A search of the medical literature was conducted using MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Scopus and Web of Science from inception to 16 March 2015. Detailed eligibility criteria for study inclusion are provided in Table 1. The search strategy had two sets of terms joined together with the ‘AND’ operator. The first included the condition of interest: ‘small intestine, intestinal diseases, bacteria, bacterial infections, blind loop syndrome, breath tests, glucose, lactulose, xylose, sucrose, irritable bowel syndrome’ (both as Medical Subject Heading terms and free text term), and ‘small bowel bacterial overgrowth, small

**Table 1 | Inclusion criteria**

Randomised controlled trials (RCTs) and observational studies using rifaximin to eradicate SIBO
Patients aged ≥18 years
Test to diagnose SIBO reported
Criteria to consider a test positive for SIBO reported
Follow-up performed to assess eradication
Rifaximin regimens reported*
Studies not including patients with neoplastic diseases

\* Studies using cyclic treatment of rifaximin or reporting more than one dosage of rifaximin tested but not indicating the number of patients treated with each dosage were not included.

intestine bacterial overgrowth, SIBO, small bowel, small intestine, malabsorption, syndromes, irritable bowel syndrome (IBS), functional diseases, HBT, glucose breath test, lactulose breath test, xylose test, sucrose breath test, jejunal aspirate' (as free text term). The second included the treatment evaluated: 'rifaximin' (as subject heading and free text term in Embase and as free text term in the other databases). A search of the abstract books from the Digestive Disease Week (2000–2014), American College of Gastroenterology (2004–2014), United European Gastroenterology Week (2000–2014), British Society of Gastroenterology (2001–2014), and Asian Pacific Digestive Week (2003–2014), was also performed. Bibliographies of all identified relevant studies were used to perform a recursive search. There were no language restrictions. Abstracts of the papers identified by the initial search were evaluated independently and in a blinded manner by the two authors for appropriateness. The primary outcome was to assess the efficacy of rifaximin to eradicate SIBO, and the secondary outcome was to evaluate its safety.

#### Data extraction

The two reviewers independently extracted data concerning the efficacy and the safety of rifaximin using predesigned data extraction forms, as dichotomous data. In addition, the following clinical data were extracted for each trial: rifaximin regimen (dose and duration), type of study (randomised controlled trial (RCT), cohort studies, etc.), type of test used to diagnose and follow-up SIBO, sample size, time between end of treatment and eradication assessment (follow-up), country where the study was carried out, concomitantly use of fibre, mesalazine, pre- or probiotics, AEs, whether the study was performed in a gastrointestinal (GI) setting, and if presence of IBS was specifically assessed. Finally, the studies reporting lower GI symptom assessment before and after treatment with rifaximin were identified and evaluated. Any disagreement was resolved by discussion between the two Authors. Distinction between cohort and case series was made according to the definition provided by Dekkers and co-workers'.<sup>17</sup> Risk of bias for RCTs was assessed as described in the Cochrane handbook.<sup>18</sup> The Newcastle–Ottawa scale (NOS, possible highest score: 9) was used to assess the quality of case–control studies if included.<sup>19</sup> Cohort studies and case series were evaluated using the 20-items quality appraisal checklist developed by the Institute of Health Economics (IHE, Canada).<sup>20</sup>

#### Data synthesis and statistical analysis

Data for primary and secondary outcomes were pooled from all kinds of studies using a random effects model as there is generally no reason to assume that trials included in the analysis are identical in the sense that the true effect size is exactly the same in all the studies.<sup>21, 22</sup> In case of cross-over studies, data from first and second period were combined, if possible. Intention-to-treat analysis (ITT) was adopted where possible. To obtain an estimate of the maximum potential benefits, a per protocol analysis was also performed.<sup>23</sup> Where possible, data from RCTs were pooled using a random effects model,<sup>21</sup> results expressed as relative risk (RR) for success of SIBO eradication, and number need to treat (NNT) calculated as described in the Cochrane handbook.<sup>24</sup> Heterogeneity between trials was assessed by  $\chi^2$  test for heterogeneity, and  $I^2$  statistic with 95% CIs was also calculated.<sup>25</sup> Its value ranges from 0% to 100%, with 0% representing no observed heterogeneity, and larger values indicating increasing heterogeneity. A value below 25% was chosen to represent low levels of heterogeneity.<sup>25</sup> When the degree of statistical heterogeneity was greater than this cut-off, for both primary and secondary outcomes, possible explanations were investigated with sub-group analysis and meta-regression, using the residual maximum likelihood with random effects weighting and the Knapp and Hartung *t*-distribution.<sup>26</sup> Prior to analysis, adjusted proportions were calculated using a logit transformation.<sup>27</sup> For the primary outcome, only studies where intention-to-treat analysis was possible were considered, and the covariates used in meta-regression and sub-group analysis were: (i) duration of treatment; (ii) dosage of rifaximin; (iii) type of study (dichotomised as RCT or no-RCT); (iv) type of test used to diagnose and follow-up SIBO; (v) sample size of the study (dichotomised as  $\geq 50$  patients vs.  $< 50$  patients); (vi) time between end of treatment and eradication assessment categorised as: within 7 days after the end of treatment; within 2–4 weeks after the end of treatment; and  $> 4$  weeks after the end of treatment; (vii) country where the study was performed (dichotomised as Italy vs. not Italy since most studies were performed in this Country); (viii) concomitantly use of fibre, mesalazine, pre- or probiotics (dichotomised as not concomitant use vs. concomitant use). For the secondary outcome, covariates used in meta-regression and sub-group analysis were: (i) duration of treatment; (ii) dosage of rifaximin; (iii) type of the study; (iv) sample size of the study; (v) country where the study was performed; (vi) concomitantly use of fibre, mesalazine, pre- or probiotics.

We also performed a sub-group analysis to evaluate the eradication rate in patients with IBS and in patients enrolled in extra-gastrointestinal settings (e.g. patients with diabetes, rosacea, etc).

Studies reporting lower GI symptom assessment before and after treatment with rifaximin were evaluated in order to identify those showing symptoms relief after therapy from those which did not.

StatsDirect v. 3.0.165 (StatsDirect, Ltd., Cheshire, UK) and STATA (StataCorp, 2013, Stata Statistical Software: Release 13.1; StataCorp LP, College Station, TX, USA) were used to generate Forest plots for primary and secondary outcomes with 95% CIs, as well as Funnel plots. The latter were assessed for evidence of asymmetry and possible publication bias or other small study effects using the Egger's linear regression.<sup>28</sup> Stata and Comprehensive Meta-Analysis v. 3.3.070 (Biostat, Inc., Englewood, NJ, USA) were used to perform meta-regression analyses.

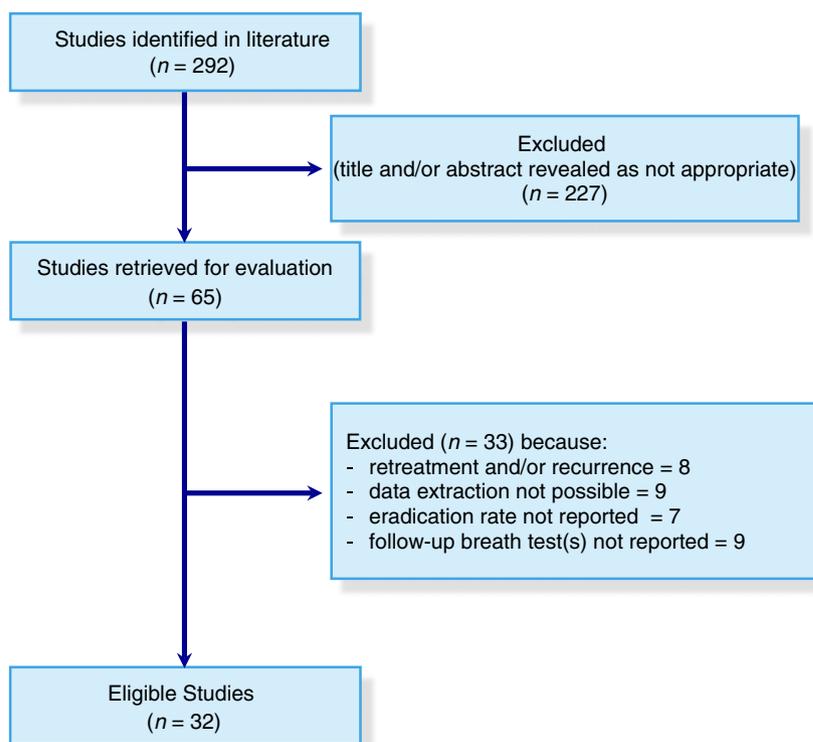
## RESULTS

The search strategy employed identified 292 citations, 227 of which were excluded after examining title and abstract. There was a total of 65 studies that were retrieved and evaluated in more detail. Of these, 33 were excluded for various reasons, leaving 32 studies<sup>29–60</sup> (2 of which were abstracts<sup>36, 54</sup>) that were eligible for inclusion involving 1331 patients as shown in Figure 1. 24 studies were cohort

studies,<sup>29, 32, 33, 35–37, 39–43, 45, 46, 49, 50, 52–60</sup> seven randomised controlled trials (RCTs).<sup>30, 31, 34, 44, 47, 48, 51</sup> Finally, one study was a randomised cross-over study<sup>38</sup>: since all patients received rifaximin (before or after placebo), they were all included in the proportion meta-analysis for pooled eradication rates and pooled AEs rate. In two studies, rifaximin was used in patients under mesalazine therapy,<sup>30, 35</sup> in other two studies, rifaximin was given to patients taking also fibres,<sup>38, 51</sup> and in one study, it was employed in association with probiotics.<sup>37</sup>

The glucose hydrogen breath test (GHBT) and the lactulose hydrogen breath test (LHBT) were used to diagnose and follow-up SIBO in 17 (53.1%),<sup>30, 31, 34, 36, 37, 40–42, 44, 48, 49, 51–54, 59, 60</sup> and 13 studies (40.6%)<sup>29, 32, 33, 35, 38, 39, 43, 45, 46, 50, 55, 57, 58</sup> respectively. Two studies<sup>47, 56</sup> used both breath tests to identify SIBO. However, only one<sup>56</sup> of those assessed also eradication by combined GHBT and LHBT.

Doses of rifaximin used ranged from 600 mg/die to 1600 mg/die, and duration of treatment ranged from 5 to 28 days. Seventy-five percentage of the studies were performed in Italy. Detailed characteristics of studies included in the meta-analysis are provided in Table S1A. No RCT was at low risk of bias (Table S1B). Quality cohort studies ranged between 10/20 and 18/20, according to quality appraisal checklist developed by the IHE<sup>20</sup>



**Figure 1** | PRISMA flow diagram of the systematic review.

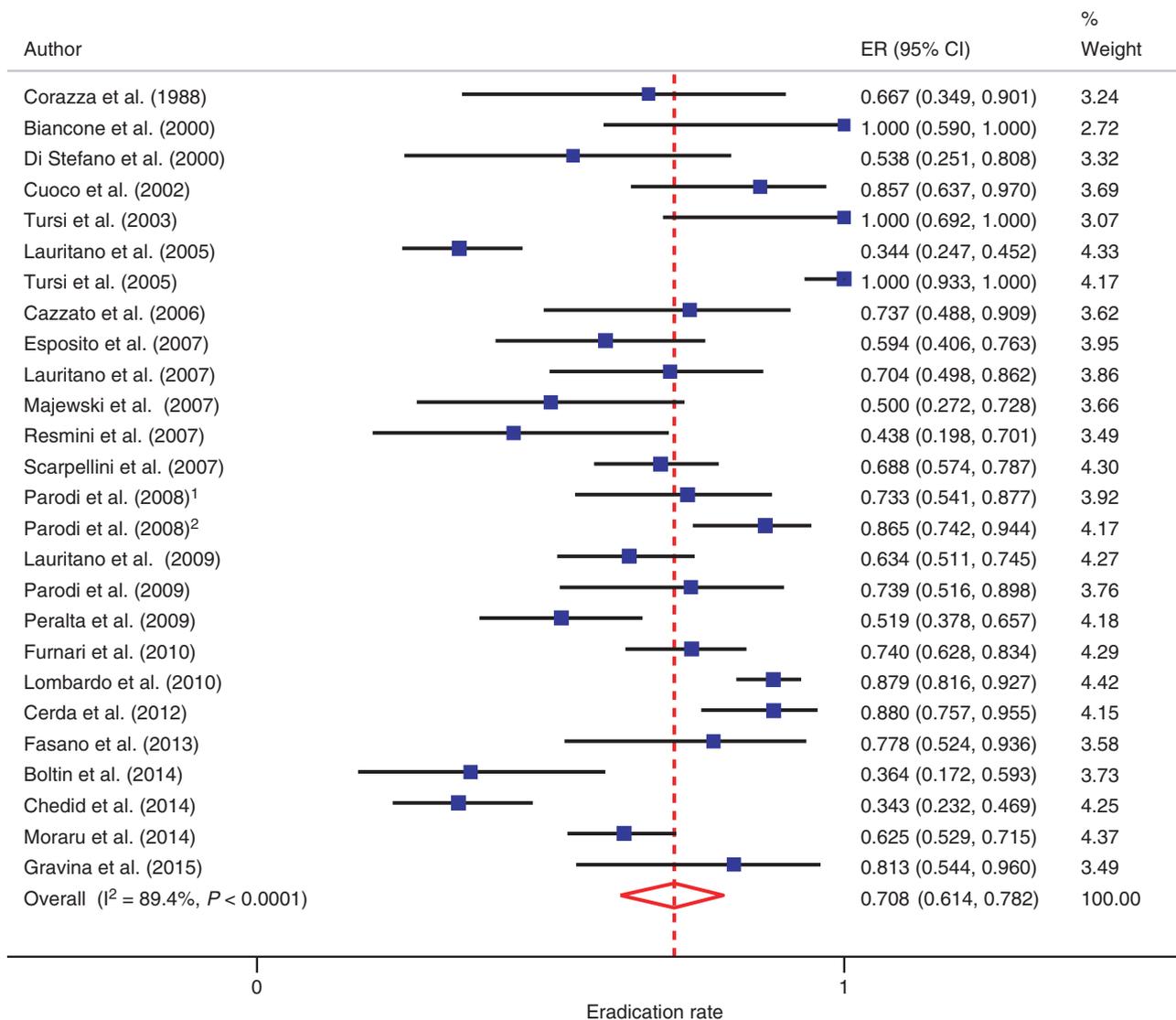
(Table S1C). ITT evaluation was possible in all but six studies.<sup>37, 38, 41, 45, 52, 55</sup>

**Overall eradication rates**

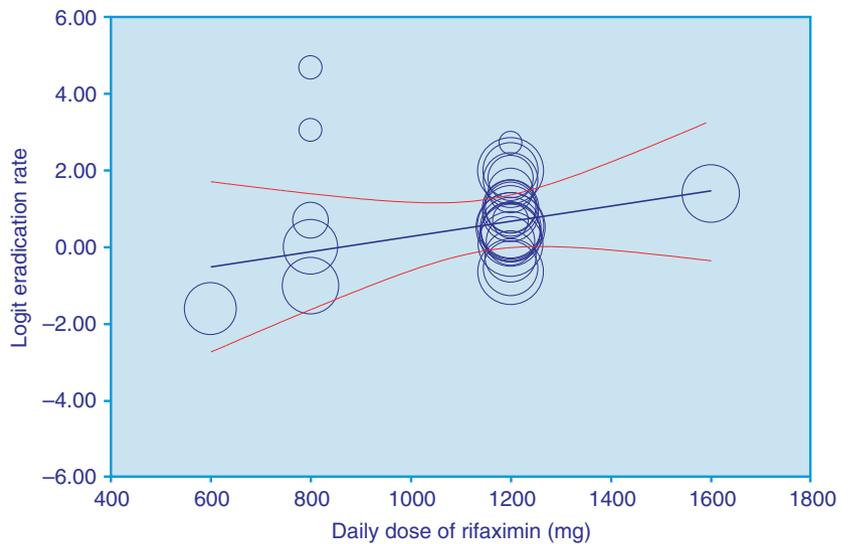
**Intention-to-treat analysis.** Intention-to-treat analysis was possible in 26 studies<sup>29–36, 39, 40, 42–44, 46–51, 53, 54, 56–60</sup> including 1141 patients. The pooled eradication rate of SIBO was 70.8% (95% CI: 61.4–78.2; Figure 2) with evidence of significant heterogeneity (Cochrane Q:  $P < 0.0001$ ;  $I^2 = 89.4\%$ ; 95% CI: 86.1–91.6), and Funnel plot asymmetry (Egger test:  $-4.16$ ; 95% CI:  $-6.40$  to  $-1.93$ ;  $P < 0.0001$ , Figure S1A). Being only two the studies where both breath tests were used,<sup>47, 56</sup> these were not included in the regression and sub-group analysis.

Meta-regression showed that eradication significantly increased for unit increase in dosage of rifaximin (Figure 3), in non-RCTs, and in studies where fibres, mesalazine, pre- or probiotics were concomitantly used with rifaximin (Table S1D). A sub-group analysis was also performed according to the same variables used for the meta-regression analysis (Table S1E).

**Per protocol analysis.** The PP analysis included overall 1274 patients from all the 32 studies (the 26 studies where ITT analysis was possible,<sup>29–36, 39, 40, 42–44, 46–51, 53, 54, 56–60</sup> and from additional 6 trials where only PP analysis could be accomplished<sup>37, 38, 41, 45, 52, 55</sup>). The pooled eradication rate of SIBO was 72.9% (95% CI: 65.5–79.8) with evidence of significant heterogeneity



**Figure 2 | Forest plot of SIBO eradication rate according to ITT analysis.**



**Figure 3 |** Meta-regression plot: logit of eradication rate vs. daily dose of rifaximin (adjusted for all the other covariates evaluated).

(Cochrane Q:  $P < 0.0001$ ;  $I^2 = 87.5\%$ ; 95% CI: 83.8–90.0), and Funnel plot asymmetry (Egger test:  $-3.47$ ; 95% CI:  $-5.28$  to  $-1.67$ ;  $P = 0.0005$ , Figures S1B and S1C).

**Eradication rates in IBS patients**

Fourteen studies<sup>37, 39, 41, 42, 44, 45, 48–50, 53–55, 58, 59</sup> were performed in patients with IBS. In 4 of them<sup>42, 44, 48, 58</sup> it was not possible to extract data concerning the SIBO eradication rate, leaving 10 studies available for the analysis.

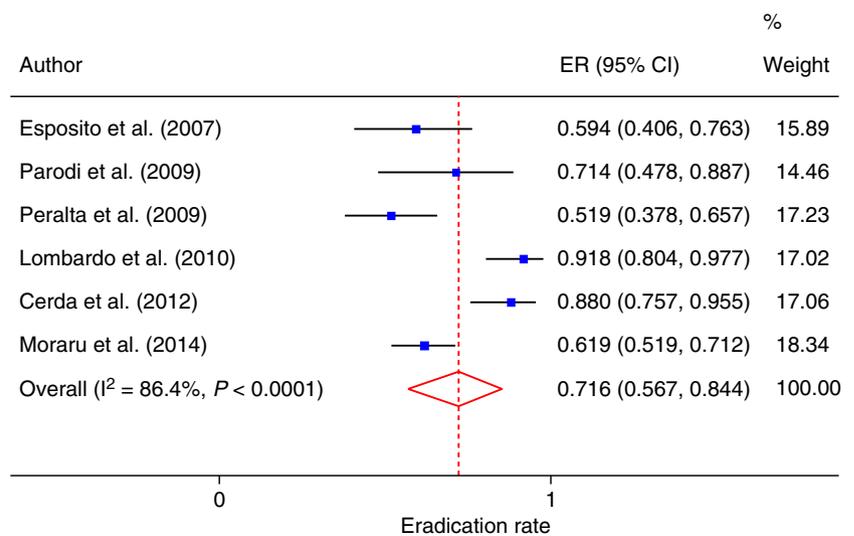
Intention-to-treat analysis was possible in six studies<sup>39, 49, 50, 53, 54, 59</sup> involving 311 patients. The pooled eradication rate of SIBO was 71.6% (95% CI: 56.7–84.4; Figure 4) with evidence of significant heterogeneity (Cochrane Q:  $P < 0.0001$ ;  $I^2 = 86.4\%$ ; 95% CI: 70.3–92.0), but without evidence of Funnel plot asymmetry

(Egger test:  $-4.80$ ; 95% CI:  $-15.4$ – $5.86$ ;  $P = 0.279$ , Figure S1D).

The PP analysis included overall 427 patients from all the 10 studies (the eight studies where ITT analysis was possible plus additional four trials where only PP analysis could be accomplished<sup>37, 41, 45, 55</sup>). The pooled eradication rate of SIBO was 75.4% (95% CI: 65.0–84.5; Figure S1E) with evidence of significant heterogeneity (Cochrane Q:  $P < 0.0001$ ;  $I^2 = 81.7\%$ ; 95% CI: 65.2–88.5), barely without evidence of Funnel plot asymmetry (Egger test:  $-3.73$ ; 95% CI:  $-7.69$ – $0.23$ ;  $P = 0.067$ , Figure S1F).

**Eradication rates in non-GI settings**

Seven studies<sup>32, 40, 43, 46, 47, 56, 60</sup> involving 182 patients were performed in non-GI settings.



**Figure 4 |** Forest plot of SIBO eradication rate in IBS patients according to ITT analysis.

According to ITT analysis, the reported overall eradication rate was 74.0% (95% CI: 62.9–83.7; Figure S1G) with evidence of significant heterogeneity (Cochrane Q:  $P = 0.0149$ ;  $I^2 = 62\%$ ; 95% CI: 0–81.4), and without evidence of Funnel plot asymmetry (Egger test:  $-3.61$ ; 95% CI:  $-7.94$ – $0.71$ ;  $P = 0.08$ ; Figure S1H).

According to PP analysis, the overall eradication rate reported was 76.8% (95% CI: 69.2–83.6; Figure S1I) without evidence of significant heterogeneity (Cochrane Q:  $P = 0.2424$ ;  $I^2 = 24.5\%$ ; 95% CI: 0–67.9), but with evidence of Funnel plots asymmetry (Egger test:  $-2.62$ ; 95% CI:  $-5.01$  to  $-0.239$ ;  $P = 0.036$ ; Figure S1J).

### Comparative studies

**Rifaximin vs. placebo.** Only one RCT<sup>47</sup> compared rifaximin alone to placebo and it was performed in patients with rosacea. 87.5% (95% CI: 71.0–96.4) of the 32 patients randomised to rifaximin were eradicated, whilst all patient ( $n = 20$ ) randomised to placebo remained positive. Those were successively treated with rifaximin and the eradication found was 85.0% (95% CI: 64.0–94.8), giving an overall eradication rate of 86.5% (95% CI: 74.2–94.4). No data on AEs were reported in this study.

**Rifaximin vs. other antimicrobials.** In two studies rifaximin (1200 mg for 7 days) was compared to chlortetracycline (333 mg t.d.s for 7 days)<sup>31</sup> or metronidazole (750 mg/die for 7 days)<sup>48</sup> respectively, including overall 168 patients. According to ITT analysis, the overall eradication rate was 61.6% (95% CI: 51.1–71.6) and 37.6% (95% CI: 21.1–55.6) in patients randomised to rifaximin and other antimicrobials respectively, with a difference in eradication rate of 24% (95% CI: 6.2–35.5) in favour of rifaximin. The pooled RR of eradicating SIBO was 1.50 (95% CI: 1.11–2.04; Figure S1K) without evidence of significant heterogeneity (Cochrane Q:  $P = 0.418$ ;  $I^2 = 0\%$ ). Egger's test was not performed due to the low number of the studies. NNT was 5 (95% CI: 2–43). According to PP analysis, the overall eradication rate was 64.6% (95% CI: 53.9–74.6) and 42.5% (95% CI: 27.7–58.6) in patients randomised to rifaximin and other antimicrobials respectively, with a difference that was not significant ( $P = 0.079$ ). The pooled RR of eradicating SIBO was 1.53 (95% CI: 0.95–2.45; Figure S1L), without evidence of significant heterogeneity (Cochrane Q:  $P = 0.256$ ;  $I^2 = 22.4\%$ ).

In the first study, there were no AEs.<sup>31</sup> In the second study,<sup>48</sup> AEs were significantly more frequent in the metronidazole (22.5%; 95% CI: 14.4–33.5) than in

rifaximin group (8.5%; 95% CI: 3.9–17.2; difference in AEs: 14.1%; 95% CI: 2.1–26). Furthermore, six patients (8.5%; 95% CI: 3.9–17.2) in the metronidazole group were obliged to discontinue the study due to the severity of AEs.

### Combination studies

**Rifaximin plus fibres.** In two studies<sup>38, 51</sup> rifaximin was given in patients taking fibres. The first one was a randomised crossover trial where patients with SIBO and symptomatic uncomplicated diverticular disease taking insoluble fibre (i.e. bran) were randomised to receive rifaximin or placebo.<sup>38</sup> The eradication rates found according to PP analysis were 83.3% (95% CI: 55.1–95.3) for rifaximin and 10% (95% CI: 1.8–40.4) for placebo with a difference in eradication significantly in favour of rifaximin (difference in eradication: 73.3%; 95% CI: 32.8–90.9). During the second phase of the study, patients not eradicated with placebo were treated with rifaximin reporting an eradication rate of 77.7% (95% CI: 39.9–97.1). The overall eradication rate (including the first and the second period) was 80.9% (95% CI: 59.9–92.3). AEs were not reported in details. However, no patient had to discontinue the study due to AEs of rifaximin.

The second study<sup>51</sup> was a RCT where patients with SIBO were randomised to receive either rifaximin alone or in combination with partially hydrolysed guar gum. The eradication rate found in the latter group was 85% (95% CI: 70.1–94.2) according to ITT analysis and 87.1% (95% CI: 72.5–95.7) according to PP analysis, and it was significantly higher than that obtained in patients treated with rifaximin alone (62.1%; 95% CI: 44.7–77.5 according to both ITT and PP analysis; difference for eradication rate according to ITT analysis: 22.8%; 95% CI: 3.18–41.5; difference for eradication rate according to PP analysis: 25%; 95% CI: 5.6–43.4).<sup>51</sup> AEs were not reported in details. However, no patient had to discontinue the study due to AEs of rifaximin.

**Rifaximin plus mesalazine.** In two studies rifaximin was given in patients taking mesalazine. The first study was a quite small RCT<sup>30</sup> where patients with Crohn's disease and SIBO were randomised to receive either rifaximin or placebo. After the end of treatment, SIBO was eradicated in all patients receiving rifaximin (100%; 95% CI: 59.0–100), and in only 28.5% (95% CI: 3.6–70.9) of those randomised to placebo (difference in eradication: 71.4%; 95% CI: 23.2–92.1). No data on AEs were reported.

The second study was performed in patients with acute uncomplicated diverticular disease of the colon<sup>35</sup> where rifaximin was able to eradicate SIBO in all patients treated (100%; 95% CI: 93.3–100).

**Rifaximin plus probiotics.** In one study<sup>37</sup> SIBO positive patients were treated with rifaximin followed by a cycle of probiotics (Lactobacilli and Bifidobacteria based preparation) for twenty-day. Follow-up was performed 4–5 months after the end of treatment and revealed an eradication rate of 82.6% (95% CI: 61.2–95). Treatment did not cause any significant AEs.

### Symptom relief

The evaluation of studies assessing symptoms before and after treatment with rifaximin (Table S1F) showed that different symptoms were measured in different ways. A thorough analysis of these studies pointed out that symptoms improved after therapy in a large proportion ( $\geq 75\%$ ) of trials, an effect seen more frequently in studies including IBS patients (Table S1F and Figure S1M). Furthermore, it was possible to extract and pool data concerning the improvement or resolution of symptoms (according to the definitions provided by the investigators) before and after eradication in only 10 trials.<sup>29, 30, 32, 33, 38, 41, 45, 46, 51, 57</sup> The overall improvement or resolution of symptoms in eradicated patients was 67.7% (95% CI = 44.7–86.9; Figure S1N), with evidence of heterogeneity (Cochrane Q:  $P < 0.0001$ ;  $I^2 = 91.3\%$ ; 95% CI: 86.9–93.7), but without Funnel plot asymmetry (Egger test: 7.97959; 95% CI: -1.290–17.249,  $P = 0.0833$ ; Figure S1O).

### Adverse events

Adverse events were reported in 17 studies involving 815 patients where only rifaximin was used.<sup>31, 32, 34, 39–44, 46, 48, 50, 53, 55–58</sup> As shown in Figure 5, the overall rate of AEs was 4.6% (95% CI = 2.3–7.5), with evidence of heterogeneity (Cochrane Q:  $P = 0.0002$ ;  $I^2 = 63.6\%$ ; 95% CI: 31.2–77.1), but without Funnel plot asymmetry (Egger test: 0.8794; 95% CI: -0.543–2.301,  $P = 0.2074$ ; Figure S1P). Meta-regression and sub-group analysis revealed that non-RCTs presented a significant lower incidence of AEs, when compared to RCTs (Table S1G and Table S1H).

Only in one study<sup>55</sup> the 0.47% (95% CI = 0.01–10.6) of patients who experience AEs had to discontinue the therapy prematurely for this reason.

A case of *C. difficile* infection (CDI) – post treatment – was reported to occur in one patient of a study were

rifaximin was used at the dosage of 1200 mg daily for 4 weeks. However, no information about either the time elapsed between the end of antibiotic therapy and the occurrence of the CDI or the presence of concurrent risk factors for the infection was provided.<sup>58</sup> The same paper reported also a case of anaphylaxis to rifaximin, again without providing any information on the severity of this AE.

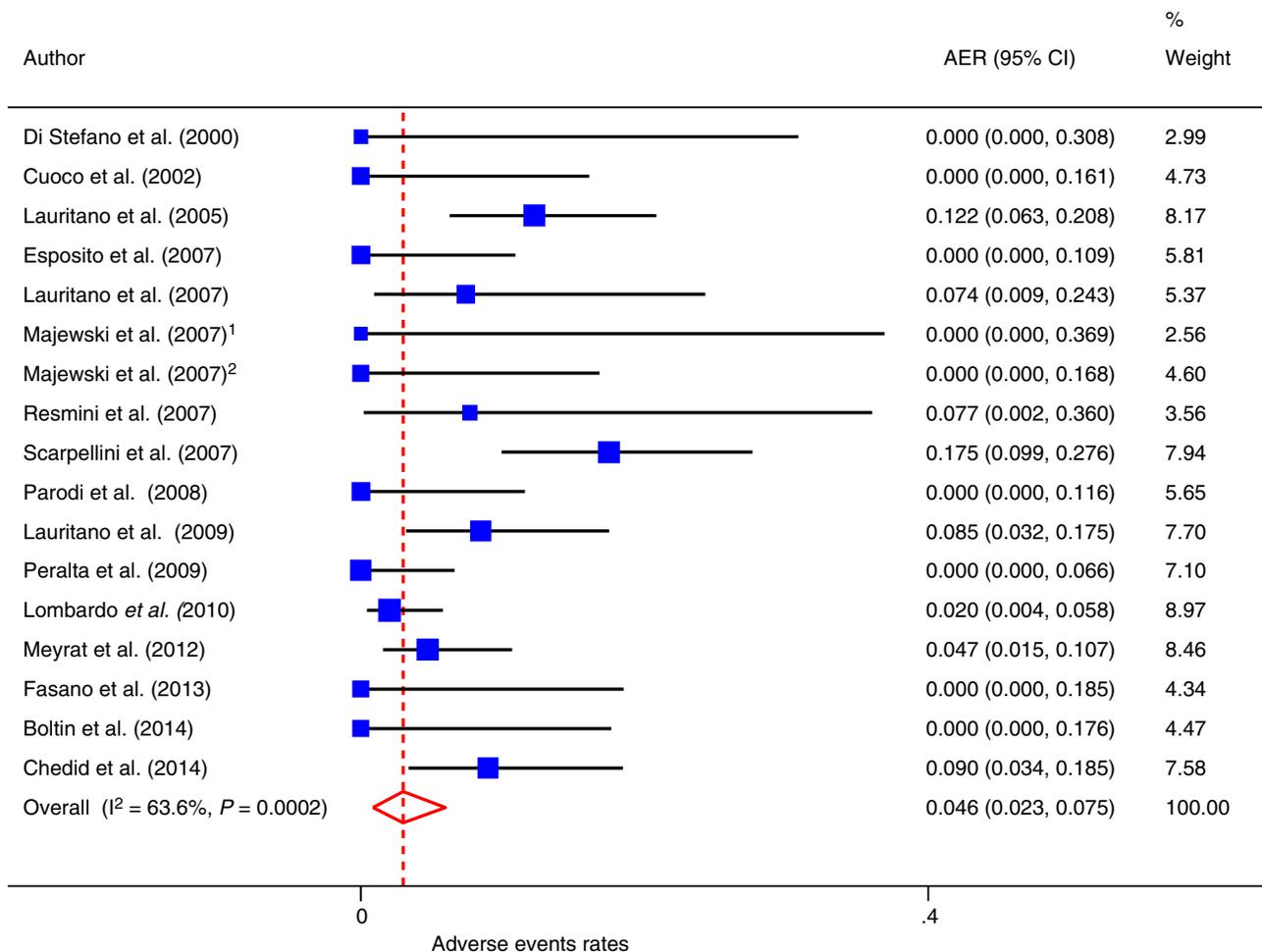
## DISCUSSION

Small intestinal bacterial overgrowth is a very heterogeneous syndrome characterised by an increased number and/or abnormal type of bacteria in the small bowel,<sup>3</sup> and is becoming a common finding in clinical practice. The management of SIBO should be centred on identifying and correcting underlying causes, treating the overgrowth, and addressing the nutrition deficiencies, where detected.<sup>3, 61</sup>

Several broad-spectrum systemic antibiotics such as fluoroquinolones, metronidazole, tetracycline, amoxicillin-clavulanic acid, chloramphenicol, etc., have been used to manage SIBO.<sup>7</sup> However, they are usually associated with several and sometimes severe AEs.<sup>61, 62</sup>

Rifaximin is a poorly absorbed antibiotic that has been largely used to treat SIBO over the past decades.<sup>10, 11</sup> Both experimental and clinical pharmacology clearly show that this compound displays a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative organisms, both aerobic and anaerobic.<sup>10, 11</sup> Being virtually non-absorbed, its bioavailability within the gastrointestinal tract is rather higher with intraluminal and faecal drug concentrations largely exceeding the minimal inhibitory concentration values observed *in vitro* against a wide range of pathogenic organism. Furthermore, it has been found that rifaximin is able to preserve colonic flora and increase the relative abundance of Lactobacilli and Bifidobacteria, showing ‘eubiotic’ effects.<sup>63, 64</sup>

The results of our meta-analysis provide evidence that rifaximin is clinically effective in eradicating SIBO. A significant heterogeneity was found and multivariate meta-regression identified three covariates (namely the drug dose, the study design and co-therapy) independently associated with an increased eradication rate. Two studies reported a dose-dependent eradication rate: the higher the daily dose of rifaximin, the higher the eradication rate.<sup>34, 44</sup> In addition, the treatment success was significantly higher in non-randomised trials.<sup>65</sup> Despite RCTs are usually preferred to evaluate the efficacy of therapeutic interventions, a large amount of evidence is



**Figure 5** | Forest plot of adverse events in patients taking rifaximin alone.

often accumulated through non-randomised studies. For this reason, we decided to include them in our analysis. It is worthwhile mentioning that RCTs and non-randomised studies show a high correlation in their estimates of efficacy. However, it is more frequent to find larger treatment effects in non-randomised studies compared to than the opposite.<sup>66–68</sup> This was indeed the case in our study. Finally, concomitant administration of rifaximin with fibres (both soluble and insoluble), probiotics (*Lactobacilli* and *Bifidobacteria*), or mesalazine, three gut microbiota-directed therapies,<sup>69–75</sup> consistently gave higher eradication rate. The global effectiveness of rifaximin in eradicating SIBO was maintained in the sub-group of patients with IBS, where a significant heterogeneity was still present. It is worth mentioning that the IBS studies were all non-RCTs.

The analysis of the studies including symptom evaluation points to an association between symptom

improvement and rifaximin treatment. It was possible to evaluate the effect of eradication on symptoms only in 10 studies. Symptoms improved or disappeared in more than two-thirds of patients (67.7%). However, the sample size was relatively small (205 patients overall) and there was also an incomplete ‘outcome bias’ since, in most studies, data regarding symptoms in non-eradicated patients were not available. Therefore, the above findings should be interpreted with caution. Nevertheless, two recent studies<sup>76, 77</sup> have shown that a positive H<sub>2</sub>BT does predict symptomatic response to antibiotic therapy in patients with IBS. A thoughtful Editorial<sup>78</sup> actually suggested that breath testing for SIBO could represent a mean to enrich rifaximin responders amongst IBS patients. By using SIBO as a biomarker of IBS, the therapeutic gain of rifaximin over placebo, reported by the TARGET trials,<sup>79</sup> may well be extended to reach a clinically significant figure.

All the studies included in our meta-analysis employed to diagnose SIBO (as well as to evaluate eradication) GHBT or LHBT, which – although widely used – are less sensitive and specific than bacterial culture, till now considered as the gold standard.<sup>6</sup> Each substrate has its own advantages and disadvantages, with GHBT favouring specificity over sensitivity, while the reverse is true for LHBT.<sup>80</sup> However, whatever breath test is used, the effectiveness of rifaximin in eradicating SIBO remains the same, as evidenced by meta-regression analysis.

Several antimicrobials have been found effective in reducing gas production, albeit with various success rates for (review see <sup>7</sup>). However, only few head to head comparisons were performed. Conversely from our study, a recent meta-analysis on antibiotic efficacy in treating SIBO narrowed the inclusion criteria to RCTs, showing that antibiotics were more effective than placebo (OR: 2.55; 95% CI: 1.29–5.04).<sup>81</sup> In their subsequent analysis on efficacy of rifaximin vs. placebo, the Authors selected three RCTs, two of which were not included in our own meta-analysis. The first trial<sup>82</sup> was performed in children whilst our study was devoted to adults only. The second study<sup>83</sup> had some methodological drawbacks. Since LHBT was performed after randomisation, patients did receive treatment independently from the presence of SIBO. Additionally, two criteria for establishing SIBO diagnosis were used, which produced significantly different results (55% positivity with the first criteria vs. 8% positivity with the second criterion). Finally, several different outcomes were adopted to evaluate rifaximin efficacy, which makes difficult to compare the results obtained with other studies.

Besides efficacy, our systematic review carefully looked at rifaximin safety and tolerability. Evidence for harms of medical interventions is important when weighting the benefits and risks of treatments in clinical decision-making. However, such evidence is often suboptimal.<sup>84, 85</sup> We found that 4.6% of patients treated with rifaximin reported AEs, but only the 0.47% of them had to discontinue the therapy. Meta-regression revealed that, among the covariates analysed, only non-RCTs were significantly associated with a lower rate of AEs when compared to RCTs. Although non-RCTs are considered conservative in estimating risks of harms (as it happened in our study), evaluation of a broad range (i.e. randomised as well non-randomised) of studies can help to build a complete picture of any potential harm and improve the generalisability of the analysis, without loss of validity.<sup>86</sup>

When considering the results of this meta-analysis, several important limitations should be acknowledged. As with any systematic review and meta-analysis, the results rely on the quality and reporting of the trials. There were no studies using culture to diagnose and follow-up the eradication. We found a significant heterogeneity among trials and for this reason meta-regression analysis was performed. However, the results of this analysis are to be interpreted with caution as meta-regression has its own limitations. Covariates used were merely related to the study design and not to the clinical condition. Furthermore, since meta-regression describes observational associations across trials, it can suffer from confounding. In addition, as the number of studies and sample size do influence the results of meta-regression, the lack of an association does not necessarily mean its 'true' absence.<sup>88</sup> The associations found in a meta-regression should therefore be considered more hypothesis-generating and not regarded as proof of causality.<sup>87, 88</sup> Only 25% of studies included in the meta-analysis were RCTs.<sup>30, 34, 38, 44, 47, 48, 51, 89</sup> No RCT resulted to be at low risk of bias, and all had problems with concealment of allocation and blinding.<sup>90</sup> Furthermore, for the sake of homogeneity, it was possible to pool the results of only two RCTs.<sup>31, 48</sup> Most of the studies included were therefore non-RCTs, which are susceptible to selection bias and, as mentioned before, tend to find larger effects.<sup>68, 91–93</sup> Moreover, data concerning the improvement or resolution of symptoms in eradicated patients were limited. Finally, funnel plots asymmetry suggested not only publication bias but the presence of other types of biases, depending on other sources (e.g. heterogeneity, poor methodological quality, etc.).<sup>94</sup> All the above limitations clearly affect the quality and the strength of the provided evidence and, therefore, the results of this meta-analysis should be considered with caution.<sup>95</sup>

In conclusion, rifaximin therapy is effective and safe for the treatment of SIBO. Since the quality of the available studies is generally poor, well-designed, large RCTs (with well-established criteria to assess SIBO and to evaluate symptoms before and after therapy according to the eradication status) are needed to substantiate these findings and to establish the optimal regimen (i.e. daily dose and duration) of rifaximin to treat this increasingly common condition.

## SUPPORTING INFORMATION

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

**Figure S1.** Figures A to P.

**Table S1.** Tables A to H.

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*Author contributions:* Luigi Gatta and Carmelo Scarpignato designed the study, did the literature search, analysed and interpreted the data, wrote and critically reviewed the paper.

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## ACKNOWLEDGEMENTS

We are indebted to Jonathan Belsey, MB BS (Sudbury, UK) for the useful suggestions dealing with the statistical approach to data

analysis. We are also grateful to the following investigators for providing us with additional data concerning their studies: Prof. R.W. McCallum (El Paso, USA), Dr L. Lombardo (Torino, Italy), Prof. M. Pimentel (Los Angeles, USA), Dr R. D'Inca (Padova, Italy), Prof. A. Gasbarrini (Rome, Italy), Dr A. De Stefano (Pavia, Italy), Dr E. Cerda (Mexico).

*Declaration of personal interests:* Dr Luigi Gatta has no conflicts of interest to disclose while Professor Carmelo Scarpignato is member of the Speakers' Bureau and of the Scientific Advisory Board of Alfa Wassermann, the manufacturer and marketer of rifaximin.

*Declaration of funding interests:* None.

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