META-ANALYSIS: LONG-TERM THERAPY WITH RIFAXIMIN IN UNCOMPPLICATED DIVERTICULAR DISEASE

Marco Bianchi, Virginia Festa, Alessandra Moretti, Antonio Ciaco, Manuela Mangone, Valentina Tornatore, Angelo Dezi, Roberto Luchetti, Barbara de Pascalis, Claudio Papi, et al.

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| Complete List of Authors: | Bianchi, Marco; ACO S.Filippo Neri, gastroenterology and Hepatology  
Festa, Virginia; ACO S.Filippo Neri, Gastroenterology and Hepatology  
Moretti, Alessandra; ACO S.Filippo Neri, Gastroenterology and Hepatology  
Ciaco, Antonio; ACO S.Filippo Neri, Gastroenterology and Hepatology  
Mangone, Manuela; ACO S.Filippo Neri, Gastroenterology and Hepatology  
Tornatore, Valentina; ACO S.Filippo Neri, Gastroenterology and Hepatology  
Dezi, Angelo; ACO S.Filippo Neri, Gastroenterology and Hepatology  
Luchetti, Roberto; ACO S.Filippo Neri, Gastroenterology and Hepatology  
De Pascalis, Barbara; ACO S.Filippo Neri, Gastroenterology and Hepatology  
Papi, Claudio; ACO S.Filippo Neri, Gastroenterology and Hepatology  
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META-ANALYSIS: LONG-TERM THERAPY WITH RIFAXIMIN IN UNCOMPPLICATED DIVERTICULAR DISEASE

Authors: Marco Bianchi, MD, Virginia Festa, MD, Alessandra Moretti, MD, Antonio Ciaco, MD, Manuela Mangone, MD, Valentina Tornatore, MD, Angelo Dezi, MD, Roberto Luchetti, MD, Barbara De Pascalis, MD, Claudio Papi, MD, Maurizio Koch, MD.

Affiliations:

Gastroenterology and Liver Unit
Azienda Ospedaliera San Filippo Neri
Via Martinotti 20, 00135 Rome – Italy

Corresponding author:

Virginia Festa, MD
Gastroenterology and Liver Unit
Azienda Ospedaliera San Filippo Neri
Via Martinotti 20, 00135 Rome – Italy
Phone: +390633062444 Fax: +390633062641

e-mail: v.festa@sanfilipponeri.roma.it

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**SUMMARY**

**Background:** Diverticular disease of the colon is a common gastrointestinal disease. Although most patients remain asymptomatic for their whole life, about 20-25% present symptoms related to “diverticular disease”. Several randomized trials verified efficacy of a poorly absorbed antibiotic, such as *rifaximin*-α (*rifaximin*), in soothing symptoms and preventing diverticulitis. **Aim** of this study is to evaluate the long-term efficacy administration of *rifaximin* plus fiber supplementation versus fiber supplementation alone, on symptoms and complications, in patient with symptomatic uncomplicated diverticular disease.

**Methods:** Pertinent studies were selected from the Medline, and the Cochrane Library Databases, references from published articles and reviews. Conventional meta-analysis according to DerSimonian and Laird method was used for the pooling of the results. The outcomes were 1- year complete symptom relief, and 1- year complication incidence. The Rate Difference (RD, with 95% CI) and the Number Needed to Treat (NNT) were used as measure of the therapeutic effect on each outcome.

**Results:** Four prospective randomized trials including 1660 patients were selected. The pooled RD for symptom relief was 29.0% (*rifaximin* vs control; 95% CI 24.5 to 33.6%; *P* < 0.0001; NNT= 3). The pooled RD for complication rate was -1.7% in favor of *rifaximin* (95% CI -3.2 to -0.1%; *P* = 0.03; NNT= 59). When considering only acute diverticulitis, the pooled RD in the treatment group was -2% (95% CI -3.4 to -0.6%; *P* = 0.0057; NNT= 50).

**Conclusions:** In symptomatic uncomplicated diverticular disease, treatment with *rifaximin* plus fiber supplementation is effective in obtaining symptom relief and preventing complications at 1 year.
INTRODUCTION

Diverticular disease of the colon is one of the most common gastrointestinal disease, with a prevalence increasing with age, from 5% of people in the fifth decade of life, to almost 50% by the ninth decade (1-3). The epidemiological dimension of the disease is sharply changing the pattern. Overall annual age-adjusted admissions for acute diverticulitis are strikingly increasing. For example, in the United States population, a 26% increase between 1998 and 2005 has been recorded (4). Rates of admission increased more rapidly within patients aged 18 to 44 years (+82%) and 45 to 74 years (+36%). Elective operations for diverticulitis rose from 16,100 to 22,500 per year during the same time period (+29%), also with a more rapid increase (73%) in rates of surgery for individuals aged 18 to 44 years. (4).

Although most patients remain asymptomatic for their whole life, about 20-25% present symptoms related to “diverticular disease” at some point (5-8). Diverticular disease can be classified in symptomatic uncomplicated disease (diverticulosis), recurrent symptomatic disease or complicated disease (9-10).

Symptomatic uncomplicated disease is characterized by abdominal pain (principally colicky left iliac fossa pain), and altered bowel habits (9,11). After a first symptomatic episode, 20% of the treated patients develop recurrent symptoms (10).

Among patients with diverticular disease, 25% develop complications, 1-2% require hospitalization and 0.5% surgery (4,11).

Acute diverticulitis is the most common complication of diverticular disease: it will develop in 10-25% of people with diverticula (3). Recurrent diverticulitis is observed in 7-42% of people with diverticular disease, and after recovery the calculated yearly risk of suffering another episode is 3% (12). Some 50% of recurrence occur within 1 year of the initial episode, and 90% occur within 5 years (13).
Haemorrhage occurs in 5-15% of patients (being severe in 3-5%) (7, 11-13). Surgery, when performed in urgency and in the septic forms like peritonitis, is loaded with a non-negligible high mortality rate, up to 26% (14-17).

Concerning medical therapy, current guidelines actually recommend only the use of high spectrum antibiotics in the initial treatment of acute diverticulitis (18). Clinical trials have provided evidence of the substantial benefit of rifaximin-alfa (rifaximin), a poor absorbable antibiotic, in diverticular disease. Indeed, available data show the efficacy of the drug in reducing symptoms in most patients with uncomplicated disease (19-23). However, its value in modifying the clinical course of the disease, and in primary prevention of diverticulitis needs to be fully quantified.

We therefore carried out a meta-analysis of randomized controlled trials (RCTs) with rifaximin plus fiber supplementation, to provide an evidence-based assessment of its potential efficacy.

The objective of this meta-analysis was to compare the efficacy of rifaximin plus fiber supplementation vs placebo on 1-year symptom disappearance and complication rate in patients with symptomatic uncomplicated diverticular disease.

METHODS

General recommendations from PRISMA revision (24) with regard to processing and reporting of results were taken into account conducting this meta-analysis (Appendix 1).

Trial Criteria

This meta-analysis includes RCTs of patients with symptomatic uncomplicated diverticular disease with the following design: rifaximin therapy, or placebo, followed by clinical re-evaluation (at least every 3 months) to assess symptom relief and complications. Cohort studies, case series, case reports were excluded.
**Literature Search**

RCTs were identified by searching MEDLINE, and the Cochrane Central Register of Controlled Trials from 1966 to September 2010. A computer-assisted search was conducted using the following combination of medical subject heading terms (MESH and not MESH terms): “diverticular disease” AND “antibiotics” AND “clinical trial”. The search strategy for PubMed used the strings: ("diverticulum"[MeSH Terms] OR "diverticulum"[All Fields] OR 
("diverticular"[All Fields] AND "disease"[All Fields]) OR "diverticular disease"[All Fields]) AND 
("anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields])
 OR "anti-bacterial agents"[All Fields] OR "antibiotics"[All Fields] OR "anti-bacterial
 agents"[Pharmacological Action]) AND ("colon"[MeSH Terms] OR "colon"[All Fields] OR
 "colonic"[All Fields]) OR ("colon"[MeSH Terms] OR "colon"[All Fields])) NOT
("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All
 Fields]). No language limits were imposed. We supplemented the electronic search by scanning the reference lists of relevant publications, including review articles and guidelines (8-10,14,25-27).

When published data were insufficient for our analyses, additional details were sought from the investigators of the corresponding clinical trials.

**Study Selection**

Our predefined inclusion criteria were: (1) prospective RCTs of treatment with poorly absorbed antibiotics versus no treatment in symptomatic colonic diverticular disease; (2) well defined outcomes including at least one of the following: (a) pain (b) complications (local and/or systemic).

The outcomes considered were the number of patients symptom free at the end of follow-up (1 year), and complications within 12 months from the first examination. So we performed a dichotomous analysis on the presence or absence of: (a) symptoms (primary outcome), (b) complications (secondary outcome). Diverticulitis was predefined as abdominal pain attributed to diverticular disease and 1 of the following criteria: (1) treated with antibiotics, hospitalization, or
surgery; or (2) described as severe or acute or presenting with fever, requiring medication, or evaluated with computed tomography. Only results fully reported in journal articles were considered. All articles passed through a multilevel, systematic review by a team of four physicians (MB, VF, AC, RL): methodological criteria and the results of each study were recorded. Studies that fulfilled the inclusion criteria were reviewed blindly and independently by the same four authors (MB, VF, AC, RL) to tabulate subject demographics, study design, definition of primary and secondary outcomes, and frequencies of each end-point, using a standardized data abstract form. Disagreement was resolved by consensus.

Assessment of risk of bias

We aimed to reduce the possibility of publication bias through searches of conference abstracts and contacting authors for any additional unreported data. An estimate of the publication bias was calculated according to Rosenthal (28).

Validity Assessment

Methodological quality was assessed independently by 2 reviewers (M.B. and V.F.) using the Cochrane risk of bias tool, an established tool based on assessing sequence generation for the randomization of subjects, allocation concealment of treatment, blinding, reporting of data, and other sources of bias (29). The methodological quality of each study was also evaluated by the same authors, using the system described by Jadad et al (30). Each study was evaluated using a 5-point scale, with 1 point being awarded for each of the following criteria: randomized controlled trial, details of randomization methods provided, double-blind study, details of blinding method provided, and information on study withdrawals provided. Discrepancies in ratings were resolved by discussion between the 2 of us. When discrepancies arose, a third party (M.K.) was consulted.
Statistical analysis

Results were analyzed by the DerSimonian–Laird method (31) for comparing and summarizing outcomes of individual RCTs. We pre-decided to use the random effect model, since it is more conservative. The term rate difference (RD), i.e. the difference in event rates between the treatment and control groups, was used as a measure of the therapeutic effect. Confidence intervals (CI) were always calculated at 95%. Number needed to treat (NNT), that is the number of patients who must be treated in order to obtain one more therapeutic effect in comparison to control group, was also calculated (32): mathematically, NNT is equivalent to the reciprocal of RD and the 95% confidence intervals for the NNT are the reciprocal of the 95% confidence intervals for RD. The alpha level was set at 0.05, for a two-tailed test. A statistical program published by T. Chalmers and us was used for this purpose (33). Results were also checked using Epistat (copyright © Epistat Services, 1991), StatsDirect statistical tools (Copyright © 1990–2001) and an appropriate meta-analysis software (34). Intertrial heterogeneity in treatment effect was evaluated using the Q statistic of DerSimonian–Laird (31), and the quantity of heterogeneity was measured using the $I^2$ (35).

To compensate somewhat for the lack of the power of the test, we decided not to accept evidence of a therapeutic effect, even if statistically significant, in the event of a $P$ value $< 0.10$ for heterogeneity. Furthermore, to detect heterogeneity, a visual display was obtained, representing the results on a L’Abbé plot (36).

RESULTS

Search Findings

The initial combined search identified 108 reports, and we excluded 80 because of the title or abstract. Of the remaining 28 articles, 24 were excluded. Nineteen had a non-randomized design. Five trials, published between 1992 and 2007, met the inclusion criteria (19-23). One of these was excluded because study design was a randomized cross-over trial (23). This review is therefore
based upon the results from four studies (19-22); for the Colecchia’s study (22) dichotomous data were obtained directly by the investigator. Upon initial analysis, concordance implied 95% agreement between the authors.

A total of 1660 patients had been enrolled: 970 were randomized to treatment with a poorly absorbed antibiotic, and 690 were randomized to no treatment. The characteristics of studies are shown in Table 1. In all studies the antibiotic used was rifaximin 400 mg bid for 7 days every month; all patients in both the treated group and control group, received a standard supplement of dietary fibers (Table 1). In only one study, control group received placebo (20).

In all studies the diagnosis of symptomatic uncomplicated diverticular disease was made by double contrast barium enema and/or colonoscopy. Clinical evaluation was performed on admission and at 2-4 months interval, for the following 12 months in 4 studies (19-21), and for 24 months in one study (22). Side effects were recorded and reported in table 2. All studies used different symptom score system based on several clinical variables. However, this review focus only the dichotomous analysis (presence/absence of any symptom).

At baseline, the specific symptoms rate were similar in both treated and control groups among all studies. The most frequent symptom was “lower abdominal pain” (range from 87.5% to 97.3% in treatment groups, and from 90.2% to 94.7% in control groups) (see Table 3).

At 1 year, the rate of patients without any symptom, as registered in the previous 6 months, ranged from 23.6% to 59.3% in control groups, and from 56.5% to 89.7% in treatment groups (Table 4). Complication rate ranged from 2.3% to 7.3% in control group, and from 0.9% to 2.3% in treatment group (Table 4).

**Quantitative data synthesis**

In all studies, the primary outcome was considered symptoms relief; complication rate was considered as a secondary outcome (15-18). Results of outcomes measures through the four studies are reported in Table 4.
Two hundred forty-one out of 690 patients in control group (pooled rate 34.9%) were symptom-free at end the follow-up, compared to 621 out of 970 patients in the treatment group (pooled rate 64.0%). The pooled RD for complete symptom relief in favor of rifaximin group was 29.0% (95% CI 24.5% to 33.6%; P < 0.0001; NNT= 3). No heterogeneity was found (Q = 1.12, d.f. = 3, P = 0.77; I² = 0%) (Figure 2).

Twenty-two out of 690 patients in control group (pooled rate 3.2%) suffered at least one complication, during 1-year follow up, compared to 15 out of 970 patients in the treatment group (pooled rate 1.5%).

A “bowel infection” occurred in 4 more patients in the control group reported in one trial (22), but they were excluded from the cumulative analysis, because possibly not related to the diverticular disease.

The pooled RD for complication rate in favor of rifaximin was -1.7% (95% CI -3.2% to -0.15%; P=0.03; NNT= 59). No heterogeneity was found (Q = 0.57, d.f. = 3, P = 0.9; I² = 0%) (Figure 3).

Considering only acute diverticulitis, 20 out of 690 patients in control group (2.8%) suffered of this complication compared to 10 out of 970 patients in the treatment group (1.0%). The pooled RD for diverticulitis rate in the treatment group was -1.9% (95% CI -3.4% to -0.57%; P =0.0057; NNT= 50) (Figure 4).

Three out of 4 trials reported side effect data (19-21). No significant difference was found between control group and treatment group.

**Bias assessment**

We did not find any evidence of publication bias. The risk of publication bias across 4 trials was investigated: the number of null studies needed to lead our meta-analysis result to a level of statistical non-significance is 148, considering the primary end-point complete symptom relief, and 4, for the secondary end-point occurrence rate of major complications (35).

The Cochrane Collaboration’s tool for assessing risk of bias is shown in Table 5.
The Jadad score is reported in Table 1. Three out of 4 trials had a score equal or higher than 3. A sufficient methodological quality was so guaranteed.

**DISCUSSION**

Most patients with colonic uncomplicated diverticular disease do not report any gastrointestinal symptoms during their lifespan; only a minority of individuals, about 20%, complain of symptoms (37). Most of the patients treated for the first episode of diverticulitis will recover and have no further clinical problems, while only 20% of these patients will develop recurrent symptoms. Consistent evidence indicates that dietary fibre, especially the insoluble fibre found mostly in fruits and vegetables rather than cereals, decreases risk of diverticula development (38,39).

The protective action of dietary fibre would make the stools bulkier, thereby increasing the colon size and decreasing intraluminal pressures, and reducing colonic transit time (40, 41).

The administration of the non-absorbable antibiotic rifaximin is able to reduce most of the clinical manifestations of diverticular disease, when compared with fiber supplementation alone. This effect is reached mainly through the reduction of the intestinal bacterial overgrowth (42). The interaction between dietary fiber and locally acting antibiotics, such as rifaximin, represents an intriguing aspect of the treatment of diverticular disease, as rifaximin has been reported to improve the clinical benefits of dietary fibers in uncomplicated diverticular disease (19-22). It has been suggested that the synergistic effect of rifaximin on a high-fiber diet may be due to a reduced proliferation of gut microflora, with a consequent decrease in bacterial hydrogen (H\textsubscript{2}) and methane (CH\textsubscript{4}) production, and/or to an expansion in fecal mass, due to a decrease in bacterial degradation of fiber, thus reducing pain (43). Furthermore, it has been suggested that these effects could induce an acceleration in intestinal transit time, thus reducing constipation, which is frequently present in patients with diverticular disease (41). Rifaximin administration was shown to be effective in
normalizing breath H\(_2\) profile in patients with intestinal bacterial overgrowth (41,43). Rifaximin absorption from the bowel is considered to be less than 1%, even in presence of colitis (44, 45).

The purpose of our meta-analysis was to evaluate the long-term efficacy administration of rifaximin plus fiber supplementation versus fiber supplementation alone, on symptoms and complications in patient with symptomatic uncomplicated diverticular disease.

The results of our study confirm previous observations, that cyclic administration of rifaximin, a poorly absorbable antibiotic, achieves symptomatic relief in a large proportions of patients with uncomplicated diverticular disease, in comparison to control. After 12 months of follow up, 64.0% (pooled rate: CI 95% 31.4 – 38.6) of patients treated with rifaximin plus standard supplement of dietary fibers were symptom-free, in comparison to 34.9% (CI 95% 60.9 – 67.0) of patients treated with fibers supplement. The 1-year gain in total symptom relief resulted statistically significant, and clinically relevant (+ 29%, NNT 3).

Although a meta-analysis does not replace a large-scale, well-designed, randomized controlled trial, individual studies may be limited by small sample sizes, especially for end points with relatively low incidences. By pooling all available data, meta-analysis allows for a more precise estimate, than that which can be obtained from the results of any individual study.

This meta-analysis has some limitations. The study overall is limited by the quality of the trials that are included. This could lead to an overestimation of the treatment effect of rifaximin. Blinding and a placebo-controlled group was guaranteed only in one study (20). Lack of heterogeneity between studies is not surprising, due to the reduced number of admitted trials. Publication bias should also be hypothesized, due to the lack of power: the number of null studies needed to lead our meta-analysis result to a level of statistical non-significance is 148, considering complete symptom relief, but is only 4, for the incidence of major complications.

This study suggests that rifaximin treatment significantly could be of value in reducing complication development: at 1 year, 1.5% of patients treated with rifaximin plus standard
supplement of dietary fibers developed complications, versus 3.2% of patients treatment with
supplement of dietary fibers.

However, the 1-year gain in primary prevention of complications was statistically, but not clinically
relevant (-1.7%; NNT 59).

Further studies would be appropriate to check if rifaximin could have a role in modifying the
clinical course of the disease, i.e. in reducing complication rate in a population with a higher
probability of the event, like patients with a previous episode of diverticulitis. In fact, one-third of
patients will proceed to a second attack of diverticulitis (46-48). Moreover, it is generally believed
that the prognosis is worse with a second attack, since some studies have reported that the rate of
complicated diverticulitis in such patients approaches 60 percent and the mortality rate is doubled
(47,49-50). Recurrent diverticulitis ranges from 7 to 42% of patients (11). Some 50% of
recurrence occur within 1 year of the initial episode (12).

Assuming the observed OR for 1-year complication rate from this meta-analysis (0.37, 95% CL
0.17-0.79), the 1-year NNT to prevent a second episode of diverticulitis could be expected to range
from 44 for a 1-year risk of 3.5% (50% of 7%, the minimum range we found in the literature) to 8
for a 1-year risk of 21% (50% of 42%, the maximum range).

In conclusion, the present meta-analysis confirms that the cyclic treatment with rifaximin plus fiber
supplementation is more effective in obtaining symptom relief and could prevent more
complications, in comparison to fiber supplementation, in symptomatic uncomplicated diverticular
disease. We conclude that the evidence that cyclic rifaximin may further reduce symptoms at 12
months, in comparison to fiber supplementation, should move from level 2 (mid-level), as indicated
in reference 51, to level 1 (meta-analysis of multiple well designed, controlled studies), according
to the Standards Committee of American Society of Colon and Rectal Surgeons (5).

However, at the moment the evidence of an effect of rifaximin over fiber supplementation on the
clinical course of diverticular disease is poor.
References


Figure legends:

Figure 1: PRISMA 2009 Flow Diagram

Figure 2: Rate differences (RD) (95% CI) for complete symptom relief at the end the follow-up in prospective randomized trials addressing Rifaximin group vs control group. Random effect model.

Figure 3: Rate differences (RD) (95% CI) for complication rate in prospective randomized trials addressing Rifaximin group vs control group. Random effect model.

Figure 4: Rate differences (RD) (95% CI) for complication rate (acute diverticulitis alone) in prospective randomized trials addressing Rifaximin group vs control group. Random effect model.

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Guarantor of the article: M. Koch

Specific author contributions:

Research design: M. Koch, M. Bianchi

Acquisition, analysis and interpretation of data: M. Koch, M. Bianchi, A. Ciaco, A. Dezi, V. Festa, R. Luchetti, M. Mangone, V. Tornatore,

Drafting the manuscript: M. Bianchi, V. Festa, A. Moretti, C. Papi, B. De Pascalis

The final draft submitted has been approved by all authors.
Figure 1

Records identified through database searching (n = 108)

Additional records identified through other sources (n = 0)

Records screened (n = 108)

Records excluded (n = 80)

Full-text articles assessed for eligibility (n = 28)

Full-text article excluded, because non randomized or cross over design (n = 24)

Studies included in qualitative synthesis (n = 4)

Studies included in quantitative synthesis (meta-analysis) (n = 4)
Figure 3

Cochrane RD (random effect)

Papi 1992

Papi 1995

Latella 2003

Collecchia

Pooled RD = -0.017 (95% CI = -0.032 to -0.0015)
Figure 4

Cochrane RD (random effect)

Pooled RD = -0.019 (95% CI = -0.034 to -0.0057)
Table 1. Studies addressing Rifaximin in the treatment of symptomatic diverticular disease

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* Rifaximin 400 mg b.i.d. for 7 days each month for 12 months
§ Dietary fiber Supplementation (20gr/die)
Table 2. Side effects recorded in patients enrolled in randomized controlled trials

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*NR= Not reported
Table 3. Baseline symptoms in patients enrolled in randomized controlled trials

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<td></td>
<td>Treatment group=84</td>
<td>97.3</td>
<td>65.3</td>
<td>88.0</td>
</tr>
<tr>
<td>Colecchia 2007</td>
<td>307</td>
<td>Controll group= 123</td>
<td>90.2</td>
<td>69.1</td>
<td>85.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group=184</td>
<td>87.5</td>
<td>71.2</td>
<td>78.0</td>
</tr>
</tbody>
</table>

*AP Abdominal Pain
Table 4. Primary end points in randomized controlled trials

<table>
<thead>
<tr>
<th>Author</th>
<th>pts</th>
<th>Randomization</th>
<th>Asymtomatic Patients n ( % )</th>
<th>Patients with complications n ( % )</th>
<th>Type of Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papi 1992</td>
<td>217</td>
<td>Controll group=110</td>
<td>26 (23.6)</td>
<td>3 (2.7)</td>
<td>3 diverticulitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group=107</td>
<td>62 (57.9)</td>
<td>1 (0.9)</td>
<td>1 recto-vaginal fistula</td>
</tr>
<tr>
<td>Latella 2003</td>
<td>968</td>
<td>Controll group= 373</td>
<td>109 (29.2)</td>
<td>12 (3.2)</td>
<td>11 diverticulitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group=595</td>
<td>336 (56.5)</td>
<td>8 (1.3)</td>
<td>1 rectal bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 diverticulitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 rectal bleeding</td>
</tr>
<tr>
<td>Papi 1995</td>
<td>168</td>
<td>Controll group= 84</td>
<td>33 (39.3)</td>
<td>2 (2.3)</td>
<td>2 diverticulitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group=84</td>
<td>58 (69.0)</td>
<td>2 (2.3)</td>
<td>2 diverticulitis</td>
</tr>
<tr>
<td>Colecchia 2007</td>
<td>307</td>
<td>Controll group= 123</td>
<td>73 (59.3)</td>
<td>9 (7.3)</td>
<td>4 diverticulitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group=184</td>
<td>165 (89.7)</td>
<td>4 (2.1)</td>
<td>1 rectal bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 intestinal infections*</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>2 diverticulitis</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 rectal bleeding</td>
</tr>
</tbody>
</table>

*Not considered in pooling analysis
Table 5  Risk of bias assessed by The Cochrane Collaboration’s tool

<table>
<thead>
<tr>
<th>Author</th>
<th>Papi</th>
<th>Papi</th>
<th>Latella</th>
<th>Colecchia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Blinding?</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Free of selective reporting</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>
Appendix 1: Prisma 2009 check-list

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td></td>
<td>Title 1 Identify the report as a systematic review, meta-analysis, or both.</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td></td>
<td>Structured summary 2 Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>2</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td></td>
<td>Rationale 3 Describe the rationale for the review in the context of what is already known.</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Objectives 4 Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>4</td>
</tr>
<tr>
<td>METHODS</td>
<td></td>
<td>Protocol and registration 5 Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eligibility criteria 6 Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>4-5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Information sources 7 Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Search 8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study selection 9 State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Data collection process 10 Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Data items 11 List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of bias in individual studies 12 Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Summary measures 13 State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>6-7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Synthesis of results 14 Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
<td>7</td>
</tr>
<tr>
<td>Section/topic</td>
<td>#</td>
<td>Checklist item</td>
<td>Reported on page #</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td>7</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>-</td>
</tr>
<tr>
<td>RESULTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study selection</td>
<td>17</td>
<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
<td>8</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td>8</td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
<td>9</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td>9</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
<td>9</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
<td>9</td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>-</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
<td>10</td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td>11</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
<td>12</td>
</tr>
<tr>
<td>FUNDING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
<td>18</td>
</tr>
</tbody>
</table>