# Long-term efficacy of rifaximin to manage the symptomatic uncomplicated diverticular disease of the colon

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#### ABSTRACT

Although rifaximin is currently advised in managing

(SUDD) of the colon, no long-term data are available.

symptomatic uncomplicated diverticular disease

This retrospective study assessed the outcome

with rifaximin, during an 8-year follow-up. The

of a large cohort of patients with SUDD, treated

study group (group A) included 346 patients with

SUDD (median age 64 years, IQR 58-69, 62.4%)

females), treated with rifaximin 800 mg/d for 7

days every month. The control group (group B)

included 470 patients with SUDD (median age 65

years, IQR 59-74 years, 60.8% females), taking

any other treatment on demand. Two symptoms

0=no symptom to 10=the most severe symptom.

(IQR) VAS score for pain was 6 (5–7) in group A

and 6 (6–7) in group B at baseline (p=0.109);

at 8-year follow-up it was 3 (3-4) and 6 (5-7),

respectively (p<0.000). Both bloating and daily

bowel movements were significantly reduced in

group A. Acute diverticulitis occurred in 9 (2.6%)

patients in group A and in 21 (4.5%) patients in

group B (p=0.155). Surgery occurred in 4 (1.2%)

(p=0.432). Disease-related mortality occurred in no

patient in group A and 2 (0.4%) patients in group B

(p=0.239). No side effects were recorded during the

Diverticulosis of the colon is the main anatom-

ical alteration detected during colonoscopy,

but the majority of people having diverticu-

losis remain asymptomatic.<sup>1</sup> The symptomatic

uncomplicated diverticular disease (SUDD) of

the colon, characterized by left lower quad-

rant pain lasting >24 hours, not fulfilling the

criteria for irritable bowel syndrome diagnosis,

and associated with raised levels of fecal calpro-

tectin,<sup>23</sup> occurs in about 20% of people having

entire study period. Rifaximin is effective to relieve

symptoms and reduce the risk of disease-related

complications in patients with SUDD.

patients in group A and 9 (1.9%) in group B

assessed by a visual analog scale (VAS), graded from

Daily bowel movements were also reported. Median

(left lower abdominal pain and bloating) were

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#### Check for updates

#### INTRODUCTION

diverticulosis.4

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#### Significance of this study

#### What is already known about this subject?

- Rifaximin is currently advised in managing symptomatic uncomplicated diverticular disease (SUDD) of the colon.
- Several studies found it effective and safe in those patients.
- No long-term data about its efficacy and safety were available.

#### What are the new findings?

- This is the longer study (8-year follow-up) ever reported.
- Rifaximin is effective and safe even in longterm use in those patients.
- It seems to be also effective in reducing disease-related complications.

## How might these results change the focus of research or clinical practice?

- Long-term cyclic treatment with rifaximin seems to be better than on-demand treatment in patients with SUDD in terms of symptoms control and safety.
- This is probably linked not to the classic antibiotic effect but to the eubiotic and anti-inflammatory effect of this nonabsorbable antibiotic.
- Long-term cyclic treatment with rifaximin could be therefore the optimal treatment in patients suffering from SUDD.

According to the statements coming from 2 recent international symposia on diverticular disease,<sup>5 6</sup> several treatments are currently available and advisable to manage SUDD. Rifaximin, a non-aminoglycoside semisynthetic non-systemic antibiotic, derived from rifamycin SV, is one of them. The main activity of rifaximin is the inhibition of bacterial protein synthesis by binding to the b-subunit of bacterial DNA-dependent RNA polymerase. This activity suppresses the RNA-chain initiation during RNA synthesis.<sup>7</sup> In vitro and in vivo, it shows a strong activity against Gram-positive and Gram-negative bacteria, both aerobic and

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anaerobic.<sup>7 8</sup> In addition, thanks to a very low systemic absorption,<sup>9</sup> its safety profile is excellent, since adverse events were observed in less than 2% of patients.<sup>10</sup>

Rifaximin has been found effective to treat SUDD symptoms. In particular, a meta-analysis found that rifaximin was significantly better than some control therapies (fiber, placebo) to treat symptoms, with an excellent number needed to treat.<sup>11</sup> However, current studies using rifaximin have a follow-up no longer than 24 months. Our aim was to assess the outcome of a large cohort of patients with SUDD, treated with rifaximin, during a long-term follow-up.

#### MATERIALS AND METHODS

We conducted a multicenter, retrospective study assessing the outcome of SUDD in all eligible patients with SUDD who had an 8-year follow-up until December 31, 2017.

Patients were considered eligible, if they had the following criteria:

- ► Have undergone colonoscopy to detect diverticulosis.
- Were at first diagnosis of SUDD. SUDD was defined as the presence of symptoms in patients with diverticulosis, in absence of signs and/or symptoms and laboratory and/or endoscopy and/or radiology evidence of acute diverticulitis, and in absence of any other complication (stenosis, abscesses, fistulas).<sup>4</sup> Moreover, presence of left lower quadrant pain >24 hours was considered the mainstay symptom to pose SUDD diagnosis.<sup>23</sup>
- Were assessed every year during an annual scheduled visit. Two symptoms (left lower abdominal pain and bloating) were assessed at each visit by a visual analog scale (VAS), graded from 0=nosymptom to 10=themost severe symptom. Bowel movements per day were also reported at each visit.
- Had given written informed consent before undergoing colonoscopy.

Patients, who met any of the following criteria, were also excluded from the study: radiological signs (by abdominal CT or by ultrasounds) of acute diverticulitis (complicated or uncomplicated); inflammatory bowel diseases and ischemic colitis; prior colonic resection; patients with severe liver failure (Child-Pugh C); patients with severe kidney failure; patients with cancer, of any origin, in treatment with radiotherapy or chemotherapy; history of constipation, alcohol, drug, or chemical abuse.

Finally, we subdivided the selected population as follows: Group A: patients who have undergone scheduled treatment with rifaximin 800 mg/d for 7 d/mo.

Group B: patients treated with short-term course (no more than 2 weeks) of symptomatic therapy (fiber, spasmo-lytics, mesalazine or other anti-inflammatory drugs, antibiotics, probiotics) only when necessary (namely only when symptoms occurred).

A shared common database was used to collect demographic and clinical data. The primary endpoint of the study was to assess the symptomatic score trend from entry (T0) to the end of follow-up (T8), in both groups and between the 2 groups.

Secondary endpoints were the comparison of acute diverticulitis occurrence between the 2 groups during follow-up, the rate of surgery occurrence between the 2 groups, the rate of disease-related between the 2 groups. The study was conducted according to the World Medical Association's Declaration of Helsinki. According to the Italian law, a formal consent is not required for this type of study.

#### Statistical methods

Statistical analyses were performed using MedCalc for Windows, V.18.2.1 (MedCalc Software, Mariakerke, Belgium). Categorical variables were expressed as absolute values and percentages, while continuous variables were expressed as median and IQR. Statistical analysis was performed using Fisher's exact test for categorical data, and the Kruskal-Wallis test for continuous data. We analyzed the probability of absence of diverticulitis occurrence during follow-up using the Kaplan-Meier method and groups were compared with the log-rank test.

All tests were two tailed, and the level of significance was 0.05.

#### RESULTS

According to the above reported criteria, a cohort of 816 patients with SUDD followed up for 8 years was identified and subdivided as follows:

Group A: 346 patients, with a median (IQR) age of 64 (58–69) years, of whom 216 (62.4%) were females.

Group B: 470 patients, with a median (IQR) age of 65 (59–74) years, of whom 286 (60.8%) were females.

No statistically significant difference was found between the 2 groups about age (p=0.546) and gender (p=0.498).

VAS score for left lower abdominal pain and bloating at baseline and at 8-year follow-up, as well as bowel movements assessment, is reported in table 1. VAS score for left lower abdominal pain and bloating, as well as bowel movements, showed a significant reduction at follow-up in group A.

Acute diverticulitis occurrence during the follow-up is reported in figure 1. It occurred in 9 patients (2.6%) in group A and in 21 patients (4.5%) in group B (p=0.155). In particular, the majority of those cases (6 out of 9 in group A and 14 out of 21 in group B) occurred within 3 years since the diagnosis of SUDD.

Surgery due to complications of the disease occurred in 4 patients (1.2%) in group A and 9 (1.9%) in group B (p=0.432). Deaths due to disease were 0 (0%) in group A and 2 (0.4%) in group B (p=0.239) (see table 2).

Table 1 Symptom score at baseline and at maximal follow-up				
Variable	Group A	Group B	P value*	
Pain				
Baseline	6 (5–7)	6 (6–7)	0.109	
Follow-up	3 (3–4)	6 (5–7)	< 0.000	
Bloating				
Baseline	3 (2–3)	2 (2–3)	< 0.000	
Follow-up	1 (0–1)	3 (2–3)	< 0.000	
Bowel movements/d				
Baseline	2 (1–3)	2 (2–3)	0.718	
Follow-up	1 (0–1)	2 (1–3)	<0.000	

Values are expressed as median (IQR) visual analog scale (VAS) score. \*Kruskal-Wallis test.



**Figure 1** Kaplan-Meier analysis of cumulative rates of absence of diverticulitis occurrence by the 2 study groups during follow-up. Log-rank test.

Significantly, all patients were fully compliant to the treatment with rifaximin, and no side effects were recorded during the entire study period.

#### DISCUSSION

According to the available guidelines,<sup>5</sup><sup>6</sup> the aim of the treatment of patients with SUDD is to have symptoms relief and to prevent complications (mainly acute diverticulitis). Different medicaments have been proposed, such as bulking agents, spasmolytics, topical antibiotics, and anti-inflammatory drugs, on the basis of different potential pathophysiological mechanisms (abnormal colonic motility, inadequate intake of dietary fibers, intestinal dysbiosis, and mucosal inflammation).<sup>4</sup> The efficacy of some treatments remains controversial. For example, fiber supplementation in the treatment of SUDD remains controversial, although it is considered a mainstay of treatment' due to the suggested beneficial effects on intestinal function related to fiber ability in holding water, increasing intraluminal colonic mass, relaxing the intestinal wall, and reducing the intraluminal pressure.<sup>4</sup>

Antibiotics are routinely used in the treatment of acute diverticulitis, even if its use in uncomplicated disease is currently under debate.<sup>9 10</sup> In SUDD, the use of antibiotics seems to have no rationale. However, rifaximin has been tested in both uncontrolled and controlled clinical studies to treat SUDD, and interesting results have been reported by a recent meta-analysis.<sup>11</sup> The mechanism, by means of which rifaximin improves symptoms in SUDD, is unclear. It has been suggested a synergistic effect of rifaximin and high fiber diet in reducing proliferation of gut microflora, with a consequent decrease in bacterial hydrogen and

Table 2Surgery occurrence and death due to the disease atmaximal follow-up				
Variable	Group A	Group B	P value*	
Surgery	4 (1.2%)	9 (1.9%)	0.432	
Death due to the disease	0 (0%)	2 (0.4%)	0.239	
*Kruskal-Wallis test.				

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methane production and/or in expanding fecal mass, due to a decrease in bacterial degradation of fibers.<sup>5 6</sup> Furthermore, its anti-inflammatory mechanism<sup>12</sup> and its new 'eubi-otic' effect<sup>13</sup> may explain its efficacy.

The studies currently available are limited to a short follow-up not exceeding 24 months. Both the larger study (>900 patients)<sup>14</sup> and the longer one (until 24 months)<sup>15</sup> found rifaximin to be effective in improving symptoms and lowering the frequency of disease complications, hypothesizing that the beneficial clinical effect of rifaximin treatment is more pronounced during the first 12 months, with efficacy lasting up to 24 months. Due to the therapeutic uncertainties about the long-term use of rifaximin, we decided to assess the effect of this drug during a long-term follow-up on a large cohort of patients with SUDD.

The present study documents several interesting findings. The first strength of this study is that we found that the quality of life of patients with SUDD is not good. Literature data on this specific topic are conflicting. Salem *et al* found that the vast majority of patients suffering from symptomatic diverticular disease described their symptoms as either absente or mild during a 5-year follow-up, and not affecting their daily activities.<sup>16</sup> More recently, we found that patients with SUDD not taking any treatment have worse abdominal pain during a 12-month follow-up.<sup>17</sup> This study found that VAS score in the control group was unchanged during the follow-up, showing clearly that the quality of life of those patients is impaired. In this way, rifaximin may be an option in controlling symptoms in those patients.

The second strength of this study is that it showed clearly that long-term cyclic treatment with rifaximin is able to control symptoms in patients with SUDD and that this effect is constant during a very long follow-up. This finding means that a scheduled treatment is more effective than an 'on demand' one, performed only when symptoms occur.

The third strength of this study is that it suggests a positive effect of rifaximin treatment on the natural history of SUDD. Until now, no definitive data are available regarding the optimal way to control symptoms and to prevent symptoms recurrence and complications occurrence.<sup>5</sup> <sup>6</sup> The present study indicates that all types of disease complications (acute diverticulitis, surgery and deaths related to the disease) seem to be lower in patients taking cyclic treatment with rifaximin than in patients taking any other on-demand treatment. The statistical significance was not reached, probably due to the low number of events occurring during the follow-up. For example, figure 1 clearly showed that cyclic treatment with rifaximin may reduce the probability of acute diverticulitis occurrence and that this effect is constant during the whole study period. Therefore, cyclic treatment with rifaximin may impact on quality of life by means of symptom control and by means of reducing the risk of complications.

The last strength of this study is that the efficacy of this therapeutic approach has been confirmed for the first time in a large population with a very long follow-up.

Moreover, rifaximin confirmed its excellent safety profile according to other studies.<sup>9 10</sup>

Obviously, this study suffers from limitations. The main one is the retrospective design. However, the large population enrolled, together with a very long observational period, compensated this limit partly. Another limit, again

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linked to the retrospective design, is that we could not assess whether some factors such as smoke or fiber consumption may have influenced the treatment efficacy, as reported in the literature dealing with the natural history of SUDD.<sup>17</sup>

In conclusion, the present study shows that cyclic administration of rifaximin is more effective than symptomatic on-demand therapies to reduce symptom persistence/recurrence and complications occurrence in patients with SUDD. Moreover, this positive effect persists during several years.

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