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Position Paper

Rifaximin and diverticular disease: Position paper of the Italian Society of Gastroenterology (SIGE)

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ABSTRACT

Management of diverticular disease has significantly improved in the last decade. Antibiotic treatment is used for symptom relief and prevention of complications. In Italy, the non-absorbable antibiotic rifaximin is one of the most frequently used drugs, and it is perceived as the reference drug to treat symptomatic diverticular disease. Its non-systemic absorption and high faecal concentrations have oriented rifaximin use to the gastrointestinal tract, where rifaximin exerts eubiotic effects representing an additional value to its antibiotic activity. This position paper was commissioned by the Italian Society of Gastroenterology governing board for a panel of experts (RC, GB, BA) to highlight the indications for treatment of diverticular disease. There is a lack of rationale for drug use for the primary prevention of diverticulitis in patients with diverticulosis; thus, rifaximin use should be avoided. The cyclic use of rifaximin, in association with high-fibre intake, is safe and useful for the treatment of symptomatic uncomplicated diverticular disease, even if the cost-efficacy of long-term treatment remains to be determined. The use of rifaximin in the prevention of diverticulitis recurrence is promising, but the low therapeutic advantage needs to be verified. No evidence is available on the efficacy of rifaximin treatment on acute uncomplicated diverticulitis.

1. Introduction

The management of diverticular disease (DD) has significantly improved over the course of the last decade. Nonetheless, several unmet demands remain. It is now clear whether clinical manifestations of diverticular disease are not uniquely represented by acute diverticulitis. Indeed, physicians in primary and specialist care are more often confronted with the management of uncomplicated patients complaining of recurrent abdominal symptoms and changes in bowel habits [1,2]. An appropriate diagnosis, classification and management of these patients is mandatory to improve their quality of life and reduce the social and economic burden of this condition. In Italy, the Scientific Association for the Study of Diverticular Disease (GRIMAD) and the Italian Society of Colorectal Surgery (SICCR) have respectively published a consensus document with a Delphi approach [3] and a guideline document for the management of DD [4]. Similar efforts have been made by Danish and Polish associations and other groups in Europe [4–6] as well as in the USA [7]. Through the critical reading of these documents, it appears evident that there is an urgent need for robust data on the epidemiology, risk factors and medical and surgical evidence-based approaches in the management of DD to create the basis for modern unifying international recommendations thatovercome the limitations of loco-regional approaches.

The treatment of DD represents a significant part of the gastroenterologist's daily practice, as noted in the national and international guidelines [3–7]. Antibiotic treatment for symptom relief and the prevention of acute complications is generally used for this condition [3–7]. In Italy, the non-absorbable antibiotic rifaximin is one of the most frequently used drugs in DD, and it is perceived as the reference drug to treat symptomatic DD. This position paper was commissioned by the Italian Society of Gastroenterology governing board for a panel of experts (RC, GB, and BA) to illustrate the current evidence and indications for the use of the non-absorbable antibiotic rifaximin in DD.

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1.1. Clinical scenarios of DD

DD is the fifth most important gastrointestinal disease in terms of health-care costs in Western countries, with the highest rates in the United States and Europe. All age groups can be affected, but prevalence increases with age, and cases in younger individuals are more likely to be complicated [8–10]. In the vast majority of individuals, colonic diverticula remain asymptomatic (diverticulosis) over their lifetime, while approximately 20% of subjects with colonic diverticula develop symptoms, including recurrent abdominal pain or discomfort, bloating, and changes in bowel habits (symptomatic diverticular disease). Only approximately 4% of patients develop acute diverticulitis, contradicting the common belief that diverticulosis has a high rate of progression [1,11].

DD is classified into four clinical stages that take into account symptoms, colonic tissue changes and complications [12,13]. STAGE I is an early phase characterized by the progressive development of colonic diverticula. In STAGE II, the patient has developed diverticula, but remains asymptomatic, a condition termed diverticulosis, which represents the most common entity. In STAGE III, approximately 20% of individuals with diverticula develop symptoms, including abdominal pain and changes in bowel habits, often indistinguishable from those of irritable bowel syndrome [14–16], which is a condition termed symptomatic uncomplicated diverticular disease (SUDD). In STAGE IV, only approximately 4% of patients develop complicated DD, including diverticulitis [1,11]. Fig. 1 shows the clinical scenarios in patients with DD, illustrating its possible natural history and estimating the prevalence for each DD stage; however, this stage classification does not imply a mandatory progression from one stage to another.

1.2. SUDD

SUDD is described by the concomitant presence of diverticula and a symptom complex characterized by abdominal pain and bloating, bowel habit changes, including diarrhoea and constipation or a mixed bowel habit. The severity and frequency of symptoms is variable and ranges from mild and rare episodes to a severe, chronic, recurrent and debilitating disorder that impacts daily activities and severely affects the quality of life of patients who have reduced vitality and emotional health [17,18]. In these patients, DD may be experienced as a chronic debilitating illness [1,17].

The symptoms of SUDD resemble those of irritable bowel syndrome (IBS) [19,20] and it is still a matter of debate whether a separation between these two conditions is always possible, as both conditions lack clear-cut diagnostic biomarkers. As a matter of fact, patients with SUDD fulfill the Rome criteria for the diagnosis of IBS in 71% of the cases [21], and the high prevalence of both IBS and colonic diverticula makes it highly probable to find the two conditions associated by chance, as shown in a cross-sectional study that reported an increased risk for diverticulosis in patients with IBS compared to those without IBS [14]. In some patients, SUDD may also follow a bout of acute diverticulitis, as shown by a recent study [22]. This condition has been termed post-diverticulitis IBS analogously to the well-known post-infectious IBS, characterized by the development of IBS symptoms in the aftermath of acute infectious gastroenteritis [22,23]. From a pathogenic standpoint, both conditions share common factors, including the participation of microbiota [20,24,25], low-grade inflammation [20], visceral hypersensitivity, gut motor dysfunction and psychological factors such as anxiety and depression [24].

A study addressing the abdominal pain patterns in DD reported that episodes of prolonged pain were frequently followed by recurrent, short-lived pain similar to that seen in IBS [25], suggesting that acute mucosal inflammation might lead to prolonged changes in gut motility and sensitivity, as described in post-infective IBS [23]. Altered patterns of colonic motility and visceral sensation similar to IBS have been described in patients with diverticulosis [26,27].

A multicentre nationwide survey reported an updated clinical picture of SUDD that was mainly characterized by unspecific symptoms, such as short-lived abdominal pain (lasting less than one day) and abdominal bloating, suggesting that SUDD has a clinical presentation similar to that of IBS [28]. An age- and gender-matched case controlled study reported that abdominal pain lasting for more than 24 h was more prevalent in patients with SUDD than in patients fulfilling the Rome III criteria for IBS (22% vs. 7%; $p < 0.01$), thus helping to discriminate a subset of patients with diverticular disease from those with IBS [29].

1.3. Acute diverticulitis

Acute diverticulitis (AD) is an inflammatory process involving one or more colonic diverticula and it is often associated with pericolonic inflammation. Complicated diverticulitis is characterized by the presence of one or more abscesses, perforations, fistulae, or colonic obstruction. Approximately 4% of patients with diverticulosis develop acute diverticulitis in their lifetime, and approximately 15% of them develop further complications such as abscesses and fistulae [11]. It has been reported that after the first episode of diverticulitis, 15–30% of patients will experience a recurrence [30–33].

Usually, the patient with AD presents with pain in the left lower quadrant of the abdomen, fever, and leukocytosis, even if many patients do not present all these symptoms at the same time [8]. Other possible symptoms or signs might include changes in bowel habits, nausea, vomiting, urinary symptoms, and elevated C reactive protein (CRP). Although diverticulitis is considered a disease of the elderly, a USA survey between 1998 and 2005 showed a marked increase in the prevalence of diverticulitis in subjects younger than 40 years [34]. In these age groups, diverticulitis predominates in males, while in those older than 65 years of age, diverticulitis appears to be more common in women [35]. According to the guidelines, in the case of a patient presenting in an acute setting with fever and laboratory findings of active inflammation, computed tomography (CT) scanning should be used to confirm the diagnosis and assess the severity of the disease as well as ruling out other disorders that can mimic diverticulitis, such as malignancy, ischaemic colitis, inflammatory bowel disease, appendicitis, and gynaecological disorders [7].

Taking into consideration the large impact of DD in Western countries and the economic burden of acute episodes, some have suggested employing therapeutic strategies aimed at preventing the first episode of diverticulitis (primary prevention), even if the cost-efficacy strategy remains largely to be determined.

1.4. Recurrent diverticulitis

In up to 25–30% of cases, AD recurs after the first episode [1,36], potentially increasing the risk of future development of recurrent abdominal pain and disturbed bowel habits (i.e., post-diverticulitis SUDD) [22]. The rate of recurrence of diverticulitis is far from being established because of the paucity of well-conducted prospective longitudinal studies. A recent retrospective longitudinal study has been carried out in the USA from 1995 to 2009, based on an analysis of the patient discharge database. In this study, 85% of patients who were managed with bowel rest and antibiotics did not have any recurrence, further suggesting that recurrent diverticulitis occurs in a minority of patients and that probably the concept that episodes of diverticulitis often recur was overemphasized in the past [37]. Generally, recurrence occurs early in the first months after the initial bout of diverticulitis and decreases thereafter [38]. Nonetheless,

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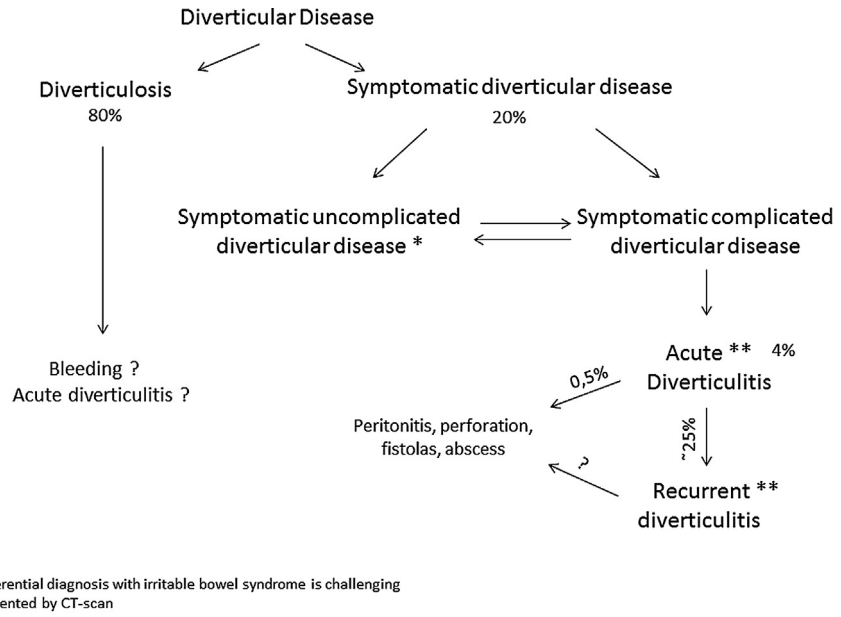

Fig. 1. Clinical scenarios of diverticular disease: hypothesized natural history and estimated prevalence for each stage.

recurrence is potentially related to complications and the need for surgery. Although predictive factors for recurrence remain poorly defined, increased serum levels of CRP (over 240 mg/l) during the first episode have been associated with early recurrence [37,38]. In a retrospective study aimed to investigate the natural history of acute diverticulitis, complicated disease recurred in 24% compared with a recurrence rate of 23% in those with uncomplicated diverticulitis ($p = 0.622$). When recurrence occurred, it usually did so within 12 months of the initial episode. Thus, these data suggest the opportunity to treat post-acute diverticulitis patients in the first 1–2 years after the episode to prevent recurrence (secondary prevention). The usefulness of long-term therapeutic management (i.e., lifetime or for more than two years) to prevent the recurrence after the first episode of AD has not been supported by any studies to date.

1.5. Rifaximin

Rifaximin was first licensed in Italy in 1985 for the treatment of a variety of gastrointestinal diseases, particularly acute bacterial diarrhoea and portal systemic encephalopathy. Rifaximin was approved for use in 33 countries under different trade names [39]. The broad spectrum of antimicrobial activity, the non-systemic absorption, and the high faecal concentrations have oriented the activity of this medication to the gastrointestinal tract [40]. Rifaximin is defined as a non-aminoglycoside semisynthetic nonsystemic antibiotic derived from rifamycin SV. Rifaximin can exert its activity through a number of different mechanisms that may go beyond the antimicrobial activity typical of antibiotics. These effects include (a) the inhibition of bacterial growth (i.e., a decrease in pathogen growth) in the small bowel with moderate minimum inhibitory concentrations (MIC) and in the colon with a low MIC and virulence; (b) the increase of resistance to bacterial infections; (c) a modulatory effect on certain bacterial species considered beneficial in the gut, including the growth of *Lactobacilli* spp. and *Bifidobacteria* spp. (so called *eubiotic effect*); (d) the modulation of bacterial metabolism, including an increase in saturated and unsaturated fatty acids and an increase in end-products of carbohydrate metabolism; and (e) anti-inflammatory activities that may go beyond the antibiotic effects and may be exerted as a specific anti-inflammatory property of rifaximin, exerted mainly through the activation of the pregnane X receptor (PXR) [41].

1.5.1. Antibiotic activities

The drug exerts its antibiotic effects through inhibition of bacterial RNA synthesis by irreversible binding to the α-subunit (RpoB) of bacterial DNA-dependent RNA polymerase [41]. The drug can reduce the virulence of bacterial enteropathogens. In sub-inhibitory concentrations, rifaximin reduces the expression of heat-stable and heat-labile enterotoxins and surface adhesion intestinal-binding factors of enterotoxigenic *Escherichia coli* (ETEC) and reduces the inflammatory response expected from virulent strains of enteroaggregative *E. coli* (EAEC) and *Shigella* [42]. The medication has in vitro antimicrobial activity against Gram-positive and Gram-negative, aerobic and anaerobic flora. The minimal inhibitory concentration for 90% of test strains (MIC90) of E. coli and other coliforms, including most non-strict anaerobic bacterial enteropathogens, is 16–32 μg/ml [43]. However, high-level rifaximin resistance (MIC90 ± 256 μg/ml) has been reported for some strains of *Campylobacter* and C. difficile [44,45].

1.5.2. Eubiotic effects

Previous data showed that the overall gut microbiota composition is not affected by rifaximin treatment [46–48]. In addition, studies indicated that rifaximin treatment promotes the growth of beneficial bacteria, such as *Bifidobacteria* and *Lactobacilli* [49] The eubiotic concept supported by these observations has been recently confirmed in culture independent metagenomic analysis carried out in an open label study on 20 patients with different gastrointestinal and liver diseases [50]. Accordingly, the study showed a significant increase in *Lactobacilli* after rifaximin treatment, persisting in a short time period and not accompanied by any significant change in the overall microbiota composition [50]. Taken together, these studies suggest that rifaximin exerts eubiotic effects that may represent an interesting additional value to its antibiotic activity.

1.5.3. Anti-inflammatory effects

Rifaximin may determine stabilization of epithelial cells and reduced gut inflammation. After pretreatment of epithelial cells with the drug, the cells continued to resist infection by adherent bacterial enteropathogens [51]. The anti-inflammatory properties

of rifaximin have been demonstrated in a study in which epithelial cells were exposed to subtherapeutic levels of rifaximin, resulting in a reduction in basal cellular levels of inflammatory cytokines [52]. Rifaximin may also exert beneficial effects in specific gastrointestinal tract disorders through a gut-specific activation of PXR [52,53]. PXR is a nuclear receptor and transcription factor involved in the modulation of drug transport and is a regulator of the inflammatory response [54]. PXR is most abundantly expressed in the small intestine and colon as well as gallbladder, liver and to a lesser extent in the stomach [55]. Studies in epithelial cell lines (Caco-2 cells) (or in vivo use of rifaximin in animal models of intestinal inflammation DSS-colitis) showed that rifaximin exerted a potent PCR-dependent anti-inflammatory activity [56]. Alteration of levels of PXR may also be associated with activity in both Crohn's disease and ulcerative colitis, which may explain the positive effect of rifaximin in inflammatory bowel disease [55,56].

1.5.4. Pharmacokinetics

Studies of faecal recovery have demonstrated less than 0.4% of detectable rifaximin in the blood and urine, undetectable levels in the bile and breast milk, and 97% recovery unchanged in the stool after oral ingestion [40]. In a study on travellers' diarrhoea (TD), the mean faecal concentration of rifaximin after 3 days of treatment with 800 mg/day was approximately 8 mg/g of faeces, and the medication remained higher than the MIC for most pathogens responsible for TD for up 6 days after treatment [57]. The activity of rifaximin against enteropathogens is thought to be due, at least in part, to its increased solubility in the presence of bile acids compared with water. Hence, rifaximin may be more active in upper GI infections because of the increased bioavailability in the small intestine compared with the aqueous setting of the colon. This may result in inhibition of a broad spectrum of bacteria in the small intestine compared with the aqueous environment of the colon, where it would have significant activity against organisms with low MIC [58]. This different solubility of rifaximin in the small intestine and colon determines a minimal negative impact on the overall gut microbiota in animal models or in humans [46]. The minimal effect on normal flora can also be explained by other mechanisms of action rather than only by direct bactericidal activity. Indeed, rifaximin was shown to transiently change the concentrations of GI bacteria during therapy and specifically reduce the concentrations of faecal coliforms in the upper gut. It also increased concentrations of the health-promoting, carbohydrate-utilizing Lactobacillus and Bifidobacterium spp., with reduction of Proteobacteria in the colon [46,47,59].

1.5.5. Dosage and mode of use

In trials on rifaximin for the treatment of DD, there has been wide heterogeneity in the dosages employed (e.g., between 400 mg to 1650 mg), continuous vs. cyclic administration (3–15 days a month each month) alone or in association with other treatments (most commonly fibre). Cyclic administration of rifaximin is supported by previous evidence indicating that the inhibition of faecal microbiota after 5 days of treatment of healthy volunteers with this nonabsorbable antibiotic at a dose of 800 mg/day is limited to the first two weeks after treatment and then recovers gradually [60,61]. In addition, rifaximin in patients with ulcerative colitis at a dose of 1800 mg/day in 3 treatment periods of 10 days each followed by 25 days of washout showed that after each washout period, concentrations of the intestinal microbiota returned to initial values, supporting the concept of cyclic administration of this compound [62]. The efficacy of long-term cyclic administration of rifaximin in SUDD has been evaluated in several long-term (12–24 months) trials [63–67]. Nonetheless, further dose finding and duration of cycles of treatment studies are now required to support the use of cyclic administration of rifaximin in SUDD.

1.5.6. Safety profile of rifaximin

The choice of a therapeutic regimen in the management of DD should always account for the efficacy of the treatment and its safety profile. These considerations are important, particularly in light of the fact that rifaximin is an antibiotic, which may theoretically increase the risk of antibiotic resistance, and may be used with the aim of treating conditions with a low risk of mortality, such as SUDD or the prevention of diverticulitis. Several studies have provided evidence that rifaximin has a high safety profile by virtue of (a) negligible systemic absorption; (b) rare bacterial chromosomal mutation; and (c) quick disappearance of resistant bacterial strains within 12 weeks after rifaximin discontinuation [61,68].

In this respect, the safety profile of the alpha polymorphic form of rifaximin (the only form marketed in Italy, as well as in many Western countries) has negligible absorption without systemic availability and thus with reduced systemic side effects [69]. Many subjects who received rifaximin as participants in five trials for the prevention or treatment of travellers' diarrhoea reported adverse events at a similar or lower frequency than subjects receiving placebo and ciprofloxacin or TMP-SMX [70–73]. No serious adverse events or deaths were reported in these clinical trials. Even clinical trials evaluating rifaximin for other gastrointestinal diseases further supported the safety and tolerability of this medication [74–77]. A recent meta-analysis derived from five studies, including 1187 patients in the treatment arm and 908 patients in the placebo arm, assessed the number needed to harm for rifaximin. On the basis of pooled analyses, the number needed to harm was 8971 with a pooled relative risk of 1.01 (95% CI, 0.50–2.02), which was not significantly different from the placebo [78]. Although similar large studies are not available in patients with DD, likely a similar safe profile of rifaximin is also reasonably expected in these patients.

1.5.7. Clinical applications

Biological effects related to these mechanisms include clinical responses in enteric infections of the small bowel and colon [79,80], reduction of small bowel bacteria and associated gas formation and improvement of symptoms associated with small intestinal bacterial overgrowth [81], including many patients with IBS [75,82], and improvement in encephalopathy [83] and reduction in gut absorption or production of ammonia, leading to reduced plasma ammonia in patients with hepatic encephalopathy [84,85] (Table 1).

The rationale for the use of rifaximin in DD is based on the assumption that faecal material entrapped in the lumen of the colonic diverticula is associated with bacterial overgrowth, mucosal low-grade inflammation and hence symptom development [86]. A recent study favours this view, as patients with DD showed an increase in mucus-degrading species (depletion of microbiota members with anti-inflammatory activity (Clostridium cluster IX, *Fusobacterium* and Lactobacillacee, *Falaecibacterium prausnitzii*) in symptomatic versus asymptomatic patients and a marked macrophage mucosal infiltration. In addition, metabolome profiles were linked to inflammatory pathways and gut neuromotor dysfunction [20]. Furthermore, Latella et al. noted that rifaximin reduced the metabolic activity of intestinal microbiota involved in the degradation of dietary fibre and the production of methane [67].

Taking into account the mentioned pharmacologic mechanisms of rifaximin, the significant clinical results in different GI diseases, and the safety profile of the molecule, rifaximin has been widely tested in the management of DD.

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Table 1
Gastrointestinal diseases or syndromes potentially treated with rifaximin and recommended treatment regimens.

Gastrointestinal disease	Recommended treatment regimen	Reference
Uncomplicated traveler's diarrhoea	200 mg t.i.d. for 3 days	[70–72]
Prevention of traveler's diarrhoea	400–550 mg once a day	[70–72]
Recurrent *Clostridium* difficile infection	400 mg t.i.d. for 2 weeks, then 200 mg t.i.d. for 2 weeks	[79,80]
Hepatic encephalopathy	550 mg t.i.d. chronically	[77,83–85]
Small bowel bacterial overgrowth	400 mg t.i.d. for 2 weeks[a]	[81]
Irritable bowel syndrome	400–550 mg t.i.d. for 2 weeks[a]	[74,82]
Inflammatory bowel diseases	400–550 mg t.i.d. and in children 10–30 mg/kg for 2–4 weeks[a]	[47,76]

[a] May require retreatment or intermittent treatment.

Table 2a
Rifaximin study in SUDD patients not included in previous systematic reviews.

Reference	Study design	Tx	No. of patients	Outcome measures	Total symtoms score 3 months vs baseline	Abdominal symptoms relief	Side effects
Stallinger et al. [91]	Open	Rifaximin 400 mg bid 7–10 days/months For 3 months	1003	Efficacy on GI global symptoms	7.2 vs 1.5 $p < 0.001$	>90% reported mild or no symptoms	24 events in 20 pts (0.6%)

Table 2b
Summary of trials evaluating the efficacy of rifaximin in the secondary prevention of acute diverticulitis not included in previous systematic reviews.

Ref.	Study design	Rifaximin vs comparator	Treatment period (months)	No. of patients	Acute diverticulitis n (%)	Side effects n (%)
Tursi et al. [94]	Open	Rifaximin 800 mg/day 1 week/month	12	109	16(18)	9/109 (08.2)
	RT	Rifaximin 800 mg/day 1 week/month + mesalazine 1600 mg/die 1 week/month		109	3 (2.7) $p < 0.01$	1/109 (0.9)
Lanas et al. [95]	Open	Rifaximin 800 mg/day 1 week/month + *Plantago ovata* 3.5 g b.d.	12	77	8 (10.4)	17/77 (22.1)
	RT	*Plantago ovata* 3.5 g b.d.		88	17 (19.3)	13/88 (14.8) $p = 0.2$
Tursi et al. [96]	Open	Rifaximin 800 mg/day 1 week/month	24	52	25%	No data
		Mesalazine 1.6 g/die		59	5% $p = 0.002$	
Festa et al. [97]	Open	Rifaximin 800 mg/day 10 days/month + *L. casei* DG 16 billion/daily for 15 days every months	14 (median)	72	7 (9.7)	No data
		Mesalazine 2.4 g/die 10 days/month + *L. casei* DG 16 billion/daily for 15 days every months		52	14 (26.9) $p = 0.015$	

2. Material and methods

The present review, performed by a task force of gastroenterologists designed by SIGE, was based on a literature search of the most relevant topics related to rifaximin and DD. These included (a) the rationale for rifaximin use in DD; (b) trials of rifaximin in SUDD and prevention of diverticulitis; and (c) the safety profile of rifaximin treatment and related side effects. Each question was answered according to the best evidence currently available following a comprehensive search of the PubMed, EMBASE, Scopus and Cochrane Library databases up to September 2016. Table 2a and 2b illustrates studies not included in the systematic reviews [87,88]. After an initial draft and various text mail exchanges, a revised text was submitted to reach the highest agreement possible. Finally, the document was externally reviewed by the SIGE Executive Board.

Question 1: Should colonic diverticulosis be treated with rifaximin?

Answer 1: No, colonic diverticulosis should not be treated with rifaximin.

Degree of evidence: Not applicable.

Supporting evidence: (a) There are no RTC nor open studies to assess rifaximin efficacy in this setting; (b) epidemiological data showed that no more than 4% of patients with diverticulosis develop diverticulitis [11,89] (see Table 3).

Explanation: Colonic diverticulosis is defined as the mere finding of diverticula in patients without abdominal complaints. The identification of diverticula in these patients is generally made as they undergo imaging or endoscopy for other indications (e.g., cancer screening). There is a lack of rationale for drug use, including rifaximin, for primary prevention of diverticulitis in patients with diverticulosis, and pharmacological intervention including rifaximin use should be avoided in this setting. Interestingly, a recent Italian primary care survey reported that 51% of patients with diverticulosis are treated with cyclic rifaximin for primary prevention of acute diverticulitis [90]. This surprising finding notes the important gap between evidence-based medicine and clinical practice in Italy.

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Table 3
Current evidence for rifaximin treatment in the diverticular disease.

	Suggestion for use	Therapeutic regimen	Level of evidence[b]	Grade of recommendation[b]
Diverticulosis	None	–	–	–
Symptomatic uncomplicated diverticular disease	Yes, with fibre supplementation	Cyclic[a] 400 mg b.i.d 12–24 month	Moderate	Conditional
Primary diverticulitis prevention	Yes, with fibre supplementation	Cyclic[a] 400 mg b.i.d 12–24 month	Low	Conditional
Secondary diverticulitis prevention	Should be determined	Cyclic[a] 400 mg b.i.d	Very low	Conditional
Uncomplicated acute diverticulitis	None	–	–	–

[a] 7–10 days a month.
[b] According to Guyatt et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64:383–94.

Question 2: Does rifaximin reduce symptoms in patients with SUDD?

Answer 2: Yes, rifaximin reduces symptoms in patients with SUDD when administered together with a high-fibre intake.

Degree of evidence: Moderate.

Supporting evidence: Two systematic reviews, one of which was a meta-analysis, suggested the usefulness of rifaximin in the treatment of SUDD, but a large randomized, placebo-controlled trial conducted according to strict modern regulatory guidance is still awaited [87,88]. In the above mentioned meta-analysis, the therapeutic regimen used was based only on cyclic treatment with rifaximin (400 bid for 7 days each month) plus high fibre intake: dietary (20 mg/day) or glucomannan (2–4 g/day) supplementation. Rifaximin was more effective in obtaining symptom relief compared with fibre alone after 12 months [65–67] and 24 months [63]. The mentioned meta-analysis found that 64% of patients treated with rifaximin plus fibre supplements were symptom free at one-year follow-up compared with 34.9% of patients treated with fibre alone. The pooled rate difference for symptom relief was 29.0% (rifaximin vs. control; 95% CI 24.5–33.6%; $p < 0.0001$; NNT = 3) [87]. After the two previous systematic reviews, only one study was found that extended the search until September 2016 (Table 2a). This non-interventional study carried out in a private practice outpatient setting involving 1,003 patients with a limited follow-up (3 months), evaluating rifaximin treatment (400 mg bid) for a period of 7–10 days. The results confirmed the beneficial effect on global gastrointestinal symptoms and showed the safe profile of cyclic rifaximin administration [91].

Explanation: According to the Italian Consensus and Guideline, it was suggested with an acceptable grade of evidence (2B) and sufficient grade of recommendation (2B) that cyclic rifaximin plus fibre supplementation should be used for a two-year course of treatment for SUDD patients for symptom relief [3]. However, the level of evidence of superiority of rifaximin over dietary fibre or fibre supplementation needs to be further assessed in large controlled studies [92] (Table 3). The cost and efficacy after two years of the cyclic treatment regimen with rifaximin in all patients with symptomatic diverticular need further investigation [88,93]. The identification of the best subgroups of patients, optimal doses, regimens, duration of cycles, association with fibre and/or the common use of probiotics between rifaximin treatments needs to be investigated.

Question 3: Does rifaximin reduce the occurrence of diverticulitis (primary prevention) in patients with symptomatic uncomplicated diverticular disease?

Answer 3: Yes, rifaximin reduces the occurrence of diverticulitis in patients with symptomatic uncomplicated diverticular disease when administered together with a high-fibre intake.

Degree of evidence: Low.

Supporting evidence: A meta-analysis suggests the potential usefulness of rifaximin treatment in the prevention of diverticulitis [87]. Four RCTs, only one of which was double-blind, studied the ability of rifaximin (added to fibre supplementation) to prevent acute diverticulitis in patients with colonic DD. When the four RCTs, for a total of 1660 patients, were included in the meta-analysis, the pooled rate difference in the treatment group was −2% (95% CI −3.4 to −0.6%; $p = 0.0057$), with a number needed to treat of 50. Considering only the double-blind, placebo-controlled 1-year trial where rifaximin (400 mg twice a day for 7 days each month) plus glucomannan (2 g/day) was compared to glucomannan alone, the results showed that both regimens were equally effective in preventing acute diverticulitis, which occurred in 2.4% of patients in both study arms [66].

Another systematic review accumulating data from placebo-controlled and unblinded trials showed that the rate of acute diverticulitis was significantly less frequent in patients treated with rifaximin plus fibre supplementation than with fibre alone 11/970 (1.1%) vs. 20/690 (2.9%) ($p = 0.012$) [88]. According to these results, the number needed to be treated to prevent an attack of acute diverticulitis in 1 year with the rifaximin plus fibre supplementation regimen reached 57 (see Table 3).

Explanation: According to the above cited data, rifaximin plus fibre may be considered more effective than fibre alone in preventing acute diverticulitis but with a low therapeutic advantage, as stated in the previous Italian consensus paper [3]. The high number needed to treat patients found together with the low number of RCTs strengthened the need to conduct large randomized, placebo-controlled trials to support the use of this therapeutic regimen in daily clinical practice.

Question 4: Does rifaximin reduce the recurrence of diverticulitis (secondary prevention) in patients with previous attacks of diverticulitis?

Answer 4: Not yet answerable.

Degree of evidence: Very low.

Supporting evidence: There are no meta-analyses addressing this specific issue. Table 2b reports the studies identified in our systematic research. The first study reported in this table compared the efficacy of a combined therapy of rifaximin and mesalazine versus rifaximin alone. This study showed that rifaximin plus mesalazine was more effective than rifaximin alone in symptom improvement and secondary prevention of recurrent diverticulitis [94]. A multicentre, randomized, open trial studied the efficacy of rifaximin (in addition to high fibre regimen) in the secondary prevention of acute diverticulitis [95]. Recurrence occurred in 10.4% of patients given rifaximin plus fibre versus 19.3% of patients receiving fibre alone ($p = 0.033$). A small open label study with 24 months follow-up and no evaluation of side effects showed that recurrence of acute diverticulitis occurred, respectively, in 25% and 5% of patients [96]. The last study reported in the table was an open label study, presented in abstract form, comparing a high dose of mesalazine (2.4 g/day for 10 days/months) plus probiotics given cyclically versus cyclic rifaximin plus probiotics (800 mg/day for 10 days/mo). Recurrence

of diverticulitis, evaluated by CT, was significantly less frequent in the rifaximin compared to the mesalazine group [97] (see Table 2b).

Explanation: Although the data suggested that cyclic administration of rifaximin could be of benefit in preventing the recurrence of acute diverticulitis, methodological limitations, heterogeneity of therapeutic regimens employed, the low number of patients and the open label design suggested that further randomized controlled studies are needed, and no recommendation for the use of rifaximin in secondary prevention of acute diverticulitis can be suggested at present.

Question 5: Is rifaximin effective in the treatment of uncomplicated acute diverticulitis?

Answer 5: No, uncomplicated acute diverticulitis should not be treated with rifaximin.

Degree of evidence: Not applicable.

Supporting evidence: In the present systematic review, no studies were identified regarding rifaximin use in uncomplicated acute diverticulitis. Thus, there are currently no available data to support its use in this condition (see Table 3).

Explanation: In clinical practice, systemic antibiotics are widely used in the management of acute diverticulitis. However, three systematic reviews [98–100] have reported no clear benefit of systemic antibiotics in uncomplicated acute diverticulitis over bowel rest and support therapy [4,101,102]. These data on the little effect of systemic antibiotics leads to the suggestion that acute diverticulitis is an inflammatory rather than an infectious condition [103]. In addition, the use of systemic antibiotic treatment is associated with several drawbacks, the most important of which are costs, adverse events, allergic reactions and antibiotic resistance [104].

A recent observational trial [102] compared the effectiveness of systemic antibiotics over observation during a first episode of uncomplicated acute diverticulitis. Five hundred twenty-eight patients were included with a median time of recovery of 14 days (i.q.r. 6–35) in the observation arm and 12 (i.q.r. 7–30) days for the antibiotic treatment strategy, with a hazard ratio for recovery of 0.91 (lower limit of 1-sided 95% CI 0.78; $p = 0.151$). No significant differences between the observation and antibiotic treatment groups were found for secondary endpoints: complicated diverticulitis, ongoing diverticulitis, recurrent diverticulitis, sigmoid resection, readmission, adverse events, and mortality. Only hospital stays were significantly shorter in the observation group (2 versus 3 days; $p = 0.006$). Observational treatment without antibiotics did not prolong recovery and can be considered appropriate in patients with uncomplicated diverticulitis.

Although no data are currently available, the peculiar mechanisms of action of rifaximin (anti-inflammatory and eubiotic activities) make this drug a potential treatment option for uncomplicated acute diverticulitis.

3. Conclusion

Treatment of DD currently poses many challenging issues for gastroenterologists, especially when faced with patients with abdominal symptoms and pain.

Along with the main clinical issues analysed by this position paper, one important indication has emerged for colonic diverticulosis (the mere finding of diverticula in patients without abdominal complaints). There is a lack of therapeutic rationale for drug use, including rifaximin, for primary prevention of diverticulitis in patients with diverticulosis, and thus rifaximin use should be avoided in this setting. The cyclic use of rifaximin, in association with high fibre intake, is safe and useful for the treatment of SUDD symptoms, even if the cost-efficacy of long-term treatment (more than 2 years) remains to be determined. The use of rifaximin plus fibre in the prevention of diverticulitis recurrence is promising, but the low therapeutic advantage calls for the need for a well-sized and robust RCT for verification. Finally, no evidence is available on the efficacy of rifaximin treatment for acute uncomplicated diverticulitis, and its therapeutic use should be avoided.

Conflict of interest

The authors have the following conflict of interest: Rosario Cuomo has served as a speaker and consultant for Alfa Wassermann, Allergan, Malesci, Almirall, Fresystem, Shire, Sofar, Biocure, Co.GE.DI, Valeas and has received research funding from Alfa Wassermann, Fresystem, Sofar, and CO.GE.DI.

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