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# Rifaximin in diverticulosis and diverticular disease: a national survey among Italian gastroenterologists and general practitioners

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## Abstract

The management of patients with diverticular disease remains challenging. The aim of this national survey was to assess how gastroenterologists and general practitioners use rifaximin to manage diverticulosis and diverticular disease. Members of the Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO) and the Italian Federation of General Practitioners (FIMMG) were invited to complete a 39-item online survey concerning the use of rifaximin in five clinical settings: (1) diverticulosis; (2) reducing symptoms in symptomatic uncomplicated diverticular disease; (3) reducing the occurrence of diverticulitis in patients with symptomatic uncomplicated diverticular disease (primary prevention); (4) reducing the recurrence of diverticulitis in patients with previous attacks of diverticulitis (secondary prevention); (5) treatment of uncomplicated acute diverticulitis. A total of 1094 physicians completed the survey. Overall, 25.1%, 83.5%, 68%, 74.2%, and 63% of physicians prescribed rifaximin for the clinical settings 1, 2, 3, 4, and 5, respectively. In each clinical setting, the dosage of rifaximin most frequently used was 800 mg/day, the most common duration of therapy was 7 days, and the cyclic administration of treatment (expressed in months) most frequently used was > 24 months. These results highlight that a reappraisal of the use of rifaximin in patients with diverticulosis and diverticular disease is required to reduce the gap between the evidence available and the daily clinical practice, optimizing also the use of healthcare resources.

**Keywords** Diverticulosis · Diverticular disease · Symptomatic uncomplicated diverticular disease (SUDD) · Diverticulitis · Treatment · Antibiotic · Rifaximin

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## Introduction

Diverticulosis is a very frequent anatomical alteration of the colon, with a global prevalence increasing in both developed and developing countries as a result of changes in diet and lifestyle [1, 2]. Diverticular disease (DD) develops when diverticulosis becomes symptomatic, and it can be considered an umbrella definition that includes different clinical conditions ranging from symptomatic uncomplicated diverticular disease (SUDD) to complicated diverticulitis. Definitions and diagnostic criteria for these entities were recently reported by an international consensus and by a state-of-the-art paper [2, 3]. Approximately 25% of individuals with diverticulosis develop symptoms, but diverticulitis occurs only in 1% of them [1, 4]. Despite diverticulitis is most common in older adults, a relative increase in diverticulitis in younger adults has been observed in recent decades [5]. Indeed, in the United States, the incidence of diverticulitis in individuals 40–49 years old increased by 132% from 1980 to 2007 [6]. Similarly, an Italian national study found that—from 2008 to 2015—the hospital admission rate for acute diverticulitis grew from 39 to 48 per 100,000 inhabitants ($p < 0.001$), and the increased rate of hospitalization accounted for patients < 60 years, remaining unchanged, during the study period, that for older patients (i.e., aged ≥ 70 years) [7].

The wide diffusion of DD in the general population—particularly in Western countries—resulted in a very high consumption of healthcare resources [8, 9]. Managing patients with DD represents a significant challenge not only for gastroenterologists (GEs) and general practitioners (GPs), but also for other clinicians, such as internal medicine or emergency physicians [2, 3, 10]. Cyclic therapy with poorly absorbed antibiotics for symptom relief and prevention of acute complications is generally adopted in some countries [4, 11–15]. Rifaximin is the most studied and used antibiotic in the setting of diverticulosis and diverticular disease [2, 4]. It is a non-aminoglycoside semisynthetic antibiotic derived from the natural antibiotic rifamycin and a structural analogue of rifampicin, characterized by the addition of a pyridoimidazole ring that makes rifaximin, a largely water-insoluble, poorly absorbable antibiotic (systemic bioavailability < 0.4% after oral administration) [16, 17]. Furthermore, rifaximin has a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative bacteria, both aerobes and anaerobes and reaching faecal concentrations some 400 times higher than minimum inhibitory concentrations (MICs) for the above microorganisms [16, 18]. However, data on the use of rifaximin in treating DD are scarce. Therefore, the Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO) and the Italian Federation of General Practitioners (FIMMG) performed a national survey among their members to gain greater insight into physicians' use of rifaximin for the management of diverticulosis and DD in daily clinical practice.

## Methods

### Questionnaire development, content, and survey distribution

The two scientific societies' (AIGO and FIMMG) promoters of the survey identified experts among their members to set up the Scientific Committee (LG, MB, CS, WM, and AC), which defined the methodology to be followed in the preparation of the survey. The study was developed in 2021 when three Italian papers on the management of DD were published: one consensus conference [11], one guideline [12], and one position paper [4]. However, only the position paper [4] was expressly devoted to elucidate the current evidence and indications for the use of rifaximin specifically in five clinical settings: (1) diverticulosis; (2) reducing symptoms in patients with SUDD; (3) reducing the occurrence of diverticulitis in patients with SUDD (primary prevention); (4) reducing the recurrence of diverticulitis in patients with previous attacks of diverticulitis (secondary prevention); (5) treatment of uncomplicated acute diverticulitis [4]. Hence, it was considered useful and worthwhile to develop a survey evaluating these five clinical settings. Nevertheless, as the study aimed to catch how rifaximin was used in real clinical practice, rifaximin regimens other than those suggested by the position paper were evaluated. The various subtypes of DD were defined according to the definitions provided by an international consensus and by a state-of-the-art paper [2, 3]. An original 39-item questionnaire was therefore developed (shown in the Supplementary Information). The survey contained general questions concerning the demographic and professional characteristics of participants. Afterwards, for each of the five clinical scenarios, participants were asked whether they used rifaximin, with what regimen (i.e., mg/day, days of therapy), if the therapy was repeated monthly, and if so, for how many months. It was also asked if rifaximin was recommended alone or together with fibres (soluble or insoluble), and/or with probiotics (used during or after the treatment with rifaximin). The first email invitation was sent on June 12, 2021, and the survey was closed on October 30, 2021.

### Participants

Eligible participants were registered members of one of the two scientific societies, for whom a valid email address was available. All data were collected anonymously.

### Statistical analysis

Continuous variables were presented as mean and standard deviation (SD). Quantitative variables were presented as absolute or relative frequencies with percentages (%). Proportions, their differences, and 95% confidence intervals (CIs) were calculated using the method recommended by Newcombe and Altman [19]. Fisher's exact test and $\chi^2$ test were used as appropriate. A multivariate logistic regression analysis was conducted to examine whether age, sex, years of profession, and geographical location of responders, as well as whether they were GEs or GPs, were potentially involved in the prescription of rifaximin: results were expressed as odds ratio (OR) with 95% CIs [20]. A two-sided-*p value* $< 0.05$ was considered significant. Stata version 16.0 was used for all analyses.

## Results

### Participants

Between June and October 2021, there were 1504 respondents: 18 refused to participate, and 392 did not complete the survey. Therefore, a total of 1094 complete questionnaires were available for the analysis, including 349 GEs and 745 GPs. Complete data on the demographic and professional characteristics of participants are shown in Table 1.

### Clinical setting 1: diverticulosis

As reported in Table 2, 25.1% of all clinicians reported to prescribe rifaximin in this setting, with a higher percentage among GPs than GEs (31.1% vs 12.3%; $p < 0.0001$). The most frequently used regimen was 800 mg/day for 7 days, and it was repeated monthly for > 24 months (16%. with no difference between GEs and GPs [$p = 0.337$]; Supplementary Information: Fig. 1). As shown in Supplementary Information: Table 2**,** the multivariate analysis showed that being GPs (OR: 2.97; $p < 0.001$) and working in the South of the country (OR: 1.77; $p = 0.003$) were independently associated with the prescription of rifaximin .

Among those who recommended rifaximin, 38.2% prescribed concomitantly fibres (no difference between GEs and GPs [$p = 0.844$]), and overall, the most frequently prescribed fibres were the soluble ones (80%), with no difference between GEs and GPs ([$p = 0.791$]; Supplementary Information: Table 3). A total of 79.6% of physicians using rifaximin prescribed it with probiotics, with more GEs than GPs preferring this association (93% vs 77.2%, $p = 0.018$). Full data for this setting are provided in Supplementary Information.

### Clinical setting 2: reducing symptoms in SUDD

Overall, 83.5% of clinicians reported to use rifaximin for this condition, with no difference between GEs and GPs ($p = 0.205$, Table 2). The most frequently used regimen was 800 mg/day for 7 days, and it was repeated monthly for > 24 months (12.9%; Supplementary Information: Fig. 2), with more GEs than GPs preferring this approach (18.3% vs 10.5%; $p = 0.001$). As shown in Supplementary Information: Table 5, the multivariate analysis showed that being male for respondents was associated with the prescription of rifaximin (OR: 1.60; $p = 0.015$). On the contrary, working in the centre (OR: 0.49; $p = 0.001$) or in the islands of the country for respondents (OR: 0.47; $p = 0.003$) was inversely associated with the prescription of rifaximin.

Among those who recommended rifaximin, 41% co-prescribed fibres concomitantly, with more GEs than GPs favouring this association (51.4% vs 36.2%; $p < 0.0001$), and overall, the most frequently prescribed fibres were the soluble ones (79.7%, with no difference between GEs and GPs [$p = 0.660$]; Supplementary Information: Table 6). A total of 80.5% of physicians using rifaximin prescribed it with probiotics (no difference between GEs and GPs [$p = 0.430$]). In detail, only 6% of all respondents prescribing rifaximin used a regimen suggested by the position paper [4] *(i.e.*, 800 mg/day for 7–10 days monthly, for 12–24 months), with no difference between GEs and GPs ($p = 0.789$). When the concomitant administration of fibres was considered, the overall adherence decreased to 2.5% with a barely not significant difference between GEs and GPs ($p = 0.053$). Full data for this setting are provided in Supplementary Information.

### Clinical setting 3: reducing the occurrence of diverticulitis in patients with SUDD (primary prevention)

As shown in Table 2, overall, 68% of clinicians reported to prescribe rifaximin for this setting, with a higher percentage of GPs than GEs (72.2% vs. 59%; $p < 0.00001$). The most frequently used regimen was 800 mg/day for 7 days, and it was repeated monthly for > 24 months (16.7%; Supplementary Information: Fig. 3), with a higher percentage of GEs than GPs choosing it (26.2% vs 13%; $p < 0.001$). As shown in Supplementary Information: Table 9, the multivariate analysis showed that being male

**Table 1** Study participant characteristics

| | Overall ($N=1094$) | GEs ($N=349$) | GPs ($N=745$) | Difference between GEs and GPs | $p$ value |
|---|---|---|---|---|---|
| Age, years (mean ± SD) | 53.4 ± 12.7 | 49.5 ± 12.8 | 55.5 ± 12.1 | −6.0% (95% CI: −7.6 to −4.4) | < 0.0001 |
| Gender | | | | | |
| Male | 41.8% | 59.0% | 57.8% | 1.2 (95% CI: −5.1 to 7.4) | 0.7138 |
| Female | 58.2% | 41.0% | 42.2% | −1.2 (95% CI: −7.4 to 5.1) | 0.7138 |
| Geographic location | | | | | |
| North | 53.1% | 47.0% | 56.0% | − 9% (95% CI: −15.3 to −2.6) | 0.006 |
| Centre | 19.3% | 20.3% | 18.8% | 1.6% (95% CI: −3.4 to 6.8) | 0.544 |
| South | 16.7% | 18.1% | 16.1% | 1.9% (95% CI: −2.7 to 7) | 0.422 |
| Islands | 10.9% | 14.6% | 9.1% | 5.5% (95% CI: 1.5 to 10) | 0.007 |
| Practice years | | | | | |
| < 5 years | 8.5% | 12.3% | 6.7% | 5.6% (95% CI: 2 to 9.8) | 0.002 |
| 5–10 years | 12.5% | 17.2% | 10.3% | 6.9% (95% CI: 2.5 to 11.6) | 0.001 |
| > 10 years | 79.0% | 70.5% | 83.0% | −12.5% (95% CI: −18.1 to−7.1) | < 0.001 |
| Employment status of GEs | | | | | |
| Public or private hospital | – | 71.4% | n.a. | n.a. | n.a. |
| Public or private university hospital | – | 18.6% | n.a. | n.a. | n.a. |
| Private practice | – | 10.0% | n.a. | n.a. | n.a. |
| For GPs: specify your type of practice | | | | | |
| I work alone | – | n.a. | 26.3% | n.a. | n.a. |
| I work with groups of 3–6 colleagues | – | n.a. | 49.3% | n.a. | n.a. |
| I work in a complex medical team (more than 6 colleagues) | – | n.a. | 24.4% | n.a. | n.a. |
| For GPs: how many patients do you have in charge/assist? | | | | | |
| < 500 patients | – | n.a. | 6.9% | n.a. | n.a. |
| 500–1000 patients | – | n.a. | 10.7% | n.a. | n.a. |
| > 1000 patients | – | n.a. | 82.4% | n.a. | n.a. |
| Do you post-graduated in gastroenterology (for GPs)? | | | | | |
| Yes | – | n.a. | 5.5% | n.a. | n.a. |
| No | – | n.a. | 94.5% | n.a. | n.a. |

*GEs* gastroenterologists, *GPs* general practitioners, *SD* standard deviation, *N* numbers, *n.a.* not applicable

(OR: 1.80; $p < 0.001$) and GPs (OR: 1.67; $p < 0.001$) for respondents was associated with the prescription of rifaximin. On the contrary, working in the islands of the country for respondents was inversely associated with the prescription of rifaximin (OR: 0.49; $p = 0.001$).

Among those who recommended rifaximin, 39.5% co-prescribed fibres concomitantly, with more GEs than GPs favouring this association (52.4% vs 34.6%; $p < 0.0001$), and overall, the most frequently prescribed fibres were the soluble ones (83.3%, with no difference between GEs and GPs [$p = 0.419$]; Supplementary Information: Table 10).

81.3% of physicians using rifaximin prescribed it with probiotics (no difference between the two groups [$p = 0.074$]). Only 6.9% of all respondents prescribing rifaximin used a regimen suggested by the position paper [4] (i.e., 800 mg/day for 7–10 days per month, for 12–24 months), with no difference between GEs and GPs ($p = 0.776$). When the concomitant administration of fibres was considered, the overall adherence decreased to 3.1%,

**Table 2** Prescription of rifaximin, fibre, and probiotics in the different clinical settings

| | Overall ($N=1094$) | | GEs ($N=349$) | | GPs ($N=745$) | | Difference between GEs and GPs | | $p$ value |
|---|---|---|---|---|---|---|---|---|---|
| | % | 95% CI | % | 95% CI | % | 95% CI | % | 95% CI | |
| **Clinical setting 1: diverticulosis** | | | | | | | | | |
| Respondents prescribing rifaximin | 25.1[a] ($N=275$) | 22.6 to 27.7 | 12.3[b] ($N=43$) | 8.9 to 15.8 | 31.1[b] ($N=232$) | 27.8 to 34.5 | − 18.8 | −23.6 to −14.0 | < 0.0001 |
| Dosage of rifaximin most frequently used: 800 mg/day | 45.1 | 39.2 to 50.0 | 53.5 | 38.6 to 68.4 | 43.5 | 37.1 to 50.0 | 10.0 | −6.2 to 26.2 | 0.231 |
| Days of treatment most frequently used: 7 days | 67.3 | 61.7 to 72.8 | 67.4 | 53.4 to 81.4 | 67.2 | 61.2 to 73.3 | 0.2 | −15.0 to 15.4 | 0.983 |
| Cyclic administration of treatment (expressed in months) most frequently used: > 24 months | 45.5 | 39.6 to 51.3 | 46.5 | 31.6 to 61.4 | 45.3 | 38.8 to 51.7 | 1.2 | −15.0 to 17.5 | 0.888 |
| Prescription of fibres with rifaximin | 38.2 | 32.4 to 43.9 | 39.5 | 24.9 to 54.1 | 37.9 | 31.7 to 44.2 | 1.6 | −14.3 to 17.5 | 0.844 |
| Use of probiotics | 79.6 | 74.9 to 84.4 | 93.0 | 81.4 to 97.6 | 77.2 | 71.7 to 82.6 | 15.8 | 6.5 to 25.2 | 0.018 |
| **Clinical setting 2: reducing symptoms in patients with SUDD** | | | | | | | | | |
| Respondents prescribing rifaximin | 83.5[a] ($N=913$) | 81.2 to 85.7 | 81.4[b] ($N=284$) | 77.3to 85.6 | 84.4[b] ($N=629$) | 81.8 to 87.0 | -3.0 | −7.9 to 1.8 | 0.205 |
| Dosage of rifaximin most frequently used: 800 mg/day | 59.5 | 56.3 to 62.7 | 70.8 | 65.5 to 76.1 | 54.4 | 50.5 to 58.3 | 16.4 | 9.8 to 23.0 | < 0.0001 |
| Days of treatment most frequently used: 7 days | 68.9 | 65.9 to 71.9 | 75.7 | 70.7 to 80.7 | 65.8 | 62.1 to 69.5 | 9.9 | 3.7 to 16.1 | 0.003 |
| Cyclic administration of treatment (expressed in months) most frequently used: > 24 months | 27.1 | 24.2 to 29.9 | 29.9 | 24.6 to 35.3 | 25.8 | 22.3 to 29.2 | 4.1 | −2.1 to 10.5 | 0.188 |
| Prescription of fibres with rifaximin | 41.0 | 37.8 to 44.1 | 51.4 | 45.6 to 57.2 | 36.2 | 32.5 to 40.0 | 15.2 | 8.2 to 22.1 | < 0.0001 |
| Use of probiotics | 80.5 | 77.8 to 82.9 | 82.0 | 77.6 to 86.5 | 79.8 | 76.7 to 82.9 | 2.2 | −3.5 to 7.5 | 0.430 |
| **Clinical setting 3: reducing the occurrence of diverticulitis in patients with SUDD (primary prevention)** | | | | | | | | | |
| Respondents prescribing rifaximin | 68.0[a] ($N=744$) | 65.2to 70.8 | 59.0[b] ($N=206$) | 53.9 to 64.2 | 72.2[b] ($N=538$) | 69.0 to 75.4 | −13.2 | −19.3 to −7.1 | < 0.0001 |
| Dosage of rifaximin most frequently used: 800 mg/day | 56.3 | 52.7 to 59.8 | 71.3 | 65.2 to 77.5 | 50.6 | 46.3 to 54.8 | 20.7 | 13.3 to 28.3 | < 0.0001 |
| Days of treatment most frequently used: 7 days | 69.8 | 66.5 to 73.1 | 75.2 | 69.3 to 81.1 | 67.7 | 63.7 to 71.6 | 7.5 | 0.5 to 14.7 | 0.044 |
| Cyclic administration of treatment (expressed in months) most frequently used: > 24 months | 36.3 | 32.8 to 39.7 | 44.1 | 37.4to 50.9 | 33.3 | 29.3 to 37.2 | 10.8 | 3.0 to 18.8 | 0.006 |
| Prescription of fibres with rifaximin | 39.5 | 36.0 to 43.0 | 52.4 | 45.6 to 59.2 | 34.6 | 30.5 to 38.6 | 17.8 | 9.9 to 25.8 | < 0.0001 |
| Use of probiotics | 81.3 | 78.4 to 84.0 | 85.4 | 80.6to 90.2 | 79.7 | 76.1 to 82.9 | 5.7 | −0.6 to 11.2 | 0.074 |
| **Clinical setting 4: reducing the recurrence of diverticulitis in patients with previous attacks of diverticulitis (secondary prevention)** | | | | | | | | | |
| Respondents prescribing rifaximin | 74.2[a] ($N=812$) | 71.5 to 76.7 | 73.9[b] ($N=258$) | 71.7 to 76.9 | 74.4[b] ($N=554$) | 71.1 to 77.4 | −0.5 | −6.1 to 5.0 | 0.849 |

**Table 2** (continued)

| | Overall ($N=1094$) | | GEs ($N=349$) | | GPs ($N=745$) | | Difference between GEs and GPs | | $p$ value |
|---|---|---|---|---|---|---|---|---|---|
| | % | 95% CI | % | 95% CI | % | 95% CI | % | 95% CI | |
| Dosage of rifaximin most frequently used: 800 mg/day | 58.4 | 55.0 to 61.8 | 70.2 | 64.6 to 75.7 | 52.9 | 48.7 to 57.0 | 17.3 | 10.3 to 24.2 | < 0.00001 |
| Days of treatment most frequently used: 7 days | 67.4 | 64.1 to 70.6 | 70.5 | 65.0 to 76.1 | 65.9 | 61.9 to 69.8 | 4.6 | −2.1 to 11.4 | 0.187 |
| Cyclic administration of treatment (expressed in months) most frequently used: > 24 months | 44.2 | 40.8 to 47.6 | 54.6 | 48.6 to 60.7 | 39.4 | .– 35.3 to 43.4 | 15.2 | 8.0 to 22.6 | < 0.00001 |
| Prescription of fibres with rifaximin | 42.6 | 39.2 to 46.0 | 51.2 | 45.1 to 57.3 | 38.6 | 34.6 to 42.7 | 12.6 | 15.2 to 19.8 | 0.008 |
| Use of probiotics | 81.2 | 78.5 to 83.4 | 82.6 | 77.9 to 87.2 | 80.5 | 77.2 to 83.8 | 2.1 | −3.6 to 7.7 | 0.486 |
| **Clinical setting 5: uncomplicated acute diverticulitis** | | | | | | | | | |
| Respondents prescribing rifaximin | 63.0[a] ($N=689$) | 60.2 to 65.9 | 37.0[b] ($N=129$) | 31.9 to 42.0 | 75.2[b] ($N=560$) | 71.9 to 78.1 | −38.2 | −43.9 to −32.1 | < 0.001 |
| Dosage of rifaximin most frequently used: 800 mg/day | 54.9 | 51.1 to 58.6 | 50.4 | 41.7 to 59.0 | 55.9 | 51.8 to 60.0 | −5.5 | −15.1 to 4.0 | 0.257 |
| Days of treatment most frequently used: 7 days | 56.9 | 53.2 to 60.6 | 49.6 | 41.0 to 58.2 | 58.6 | 14.2 to 20.5 | −9.0 | −18.5 to 0.6 | 0.064 |
| Monthly treatment cycles most frequently used: 2 months | 41.8 | 38.1 to 45.5 | 38.0 | 29.6 to 46.4 | 42.7 | 38.6 to 46.8 | −4.7 | −14.0 to 4.6 | 0.323 |

*GEs* gastroenterologists, *GPs* general practitioners, *N* numbers, *mg* milligrams, *SUDD* symptomatic uncomplicated diverticular disease

[a]Proportion of respondents reporting to prescribe rifaximin out of the total number of all respondents to the survey expressed as percentage

[b]Proportion of GEs/GPs reporting to prescribe rifaximin out of the total number of all GEs/GPs who responded to the survey expressed as percentage

with more GEs than GPs preferring this association (5.8% vs 2%; $p=0.008$). Full data for this setting are provided in Supplementary Information.

## Clinical setting 4: reducing the recurrence of diverticulitis in patients with previous attacks of diverticulitis (secondary prevention)

Among all the responders, 74.2% of clinicians reported prescribing rifaximin for this setting, with no difference between GEs and GPs ($p=0.849$, Table 2). The most frequently used regimen was 800 mg/day for 7 days, and it was repeated monthly for > 24 months (20.2%; Supplementary Information: Fig. 4), with a higher percentage of GEs than GPs choosing it (27.5% vs 16.8; $p<0.001$).

As shown in Supplementary Information: Table 13, the multivariate analysis showed that the age of respondents (OR: 1.02; $p=0.016$) and being male (OR: 1.59; $p=0.003$) were independently associated with the prescription of rifaximin. On the contrary, working in the centre (OR: 0.65; $p=0.022$) and in the islands of the country for respondents (OR: 0.41; $p<0.001$) was inversely associated with the prescription of rifaximin.

Among those who recommended rifaximin, 42.6% co-prescribed fibres concomitantly, with more GEs than GPs favouring this association (51.2% vs 38.6%; $p=0.008$), and overall, the most frequently prescribed fibres were the soluble ones (80.9%, with no difference between GEs and GPs [$p=0.817$]; Supplementary Information: Table 14). 81.2% of physicians using rifaximin prescribed it with probiotics (no difference between GEs and GPs [$p=0.486$]). Full data for this setting are provided in Supplementary Information.

### Clinical setting 5: use in the treatment of uncomplicated acute diverticulitis

As reported in Table 2, 63% of all clinicians reported to prescribe rifaximin for treating patients with acute diverticulitis, with a higher percentage of GPs than GEs (75.2% vs 37%, $p < 0.001$). The most frequently used regimen was 800 mg/day for 7 days (12.6%; Supplementary Information: Fig. 5). As shown in Supplementary Information: Table 16, the multivariate analysis showed that only being GPs for respondents was independently associated with the prescription of rifaximin (OR 4.78; $p < 0.001$). Full data for this setting are provided in Supplementary Information.

## Discussion

The prevalence of diverticulosis and diverticular disease is increasing in both developed and developing countries [2, 21, 22]. At the same time, there is an increase in hospitalizations for diverticular disease and diverticulitis, with a consequent increase in workload for both gastroenterologists and general internal medicine physicians [7, 23–25].

To the best of our knowledge, this is the first national survey performed among GEs and GPs specifically committed to assess if and how (dose, duration, of treatment, etc.) physicians prescribe rifaximin in patients with diverticulosis and DD. Being in Italy, the position paper published by the Italian Society of Gastroenterology and Digestive Endoscopy (SIGE), expressly devoted to evaluating the current evidence for using rifaximin in these conditions, was chosen as a benchmark (Table 3) [4]. In this paper, the experts suggested the use of rifaximin in combination with fibre in only two out of the five clinical settings considered: reducing symptoms in SUDD (clinical setting 2), and reducing the occurrence of diverticulitis in patients with SUDD-primary prevention (clinical setting 3).

In the former case (setting 2), our survey found that > 80% of all respondents prescribed rifaximin, without difference between GEs and GPs. The overall adherence of respondents to the dose and duration of therapy recommended by the position paper (i.e., 800 mg/day for 7–10 days) [4] was greater among GEs (87.6% vs 78.1, respectively, $p$ for difference = 0.004; data not shown). When the cyclic administration of rifaximin (expressed in months) was considered, it was unexpectedly found that the most frequent choice was > 24 months (overall 27.1%, with no difference between GEs and GPs).

In the latter case (setting 3), rifaximin was used by 68% of overall physicians, with a significantly higher percentage of prescribers among GPs than GEs ($p < 0.001$). The overall adherence of respondents to the dose and duration of therapy recommended by the position paper (i.e., 800 mg/day for 7–10 days) [4] was similar among GEs (85.7%) and GPs (78.7%, $p$ for difference = 0.079; data not shown). Even in this instance, when the cyclic administration of rifaximin was considered, it was unexpectedly found that the most frequent choice was > 24 months (overall 36.3%, with a significantly higher percentage of GEs preferring this option compared to the GPs). The diagnosis of SUDD remains a challenge for clinicians. A recent International Consensus provided a definition and diagnostic criteria for this entity [3]. However, the consensus level of agreement was only 49.19% for 'A+', and the overall statement was graded as EL: 1c and RG: B1.

**Table 3** Indication for rifaximin treatment in the diverticular disease (modified from Cuomo et al. [4])

| | Suggestion for use of rifaximin | Therapeutic regimen of rifaximin | Suggestion for use of fibre supplementation | Level of evidence[a] | Grade of recommendation[a] |
|---|---|---|---|---|---|
| Diverticulosis | No | – | – | – | – |
| Reducing symptoms in SUDD | Yes | 400 mg bid for 7–10 days a month, for 12–24 months | Yes | Moderate | Conditional |
| Reducing the occurrence of diverticulitis in patients with SUDD (primary prevention) | Yes | 400 mg bid for 7–10 days a month, for 12–24 months | Yes | Low | Conditional |
| Reducing the recurrence of diverticulitis in patients with previous attacks of diverticulitis (secondary prevention) | Should be determined | 400 mg bid for 7–10 days | Should be determined | Very low | Conditional |
| Uncomplicated acute diverticulitis | No | – | – | – | – |

*SUDD* symptomatic uncomplicated diverticular disease, *bid* bis in die, *mg* milligrams

[a]According to Guyatt et al. [59]

Indeed, a recent study found a significant diagnostic delay in patients with SUDD (both patient and physician-dependent), IBS being the most frequent misdiagnosis [10], especially because of the overlapping symptom cluster [26, 27]. Finally, it is worth reminding that there are some discrepancies in the recommendations of rifaximin for clinical settings 2 and 3 when other international guidelines are considered [3, 4, 11, 12, 14, 28–33].

The adherence to the co-prescription of rifaximin with fibres was overall low (< 50%) for both clinical settings 2 and 3, although a significantly higher percentage of GEs than GPs used this association, and ≥ 80% of all respondents preferred to use soluble fibre. This might be due to the fact that in several studies where rifaximin was combined with fibres, these were soluble (mainly glucomannan) [34–38].

Overall, for settings 2 and 3, only 6% and 6.9% of all respondents recommended rifaximin using a regimen—i.e., dose, duration, and cyclic administration—suggested by the position paper [4], respectively. These figures were further reduced when the concomitant administration of fibres was considered, as only 2.5% and 3.1% of participants adhered to this recommendation [4] for settings 2 and 3, respectively, emphasizing the importance of reducing the gap between literature evidence and daily clinical practice.

In the remaining three settings evaluated in the position paper (namely diverticulosis, reducing the recurrence of diverticulitis in patients with previous attacks of diverticulitis [secondary prevention], and treatment of uncomplicated acute diverticulitis), experts, as well as guidelines, did not recommend the use of rifaximin [2–4, 11, 12, 14, 28–33]. Yet, the survey reported surprising findings. Indeed, it was found that among the overall respondents, adherence to these recommendations was poor 25.1% of physicians prescribed rifaximin in diverticulosis, 74.2% for secondary prevention, and 63% for the treatment of uncomplicated diverticulitis. GPs prescribed rifaximin more frequently than GEs for diverticulosis and for the treatment of uncomplicated diverticulitis, while in the remaining setting, there was no difference between the two groups. Furthermore, in diverticulosis and secondary prevention, the cyclic administration of rifaximin most frequently chosen by the overall respondent was > 24 months. The reasons for this poor adherence to recommendations are not clear. However, although the evidence that rifaximin in secondary prevention is low [38, 39], its symptom-relieving activity [40, 41] in a clinical condition of ongoing intestinal inflammation [42–44] is still high. Our study was, however, a survey and, therefore, not conceived to discover the rationale behind the physicians' prescriptions. Concerning diverticulosis, it could be speculated that physicians might perceive this condition as a risk factor [2]. Yet, a retrospective study over an 11-year follow-up period clearly found that only 4.3% of patients with diverticulosis at baseline developed acute diverticulitis [45]. Likewise, although some data seem to suggest that cyclic administration of rifaximin could be of benefit for secondary prevention, the low quality of the evidence does not allow rifaximin to be recommended [2–4, 11, 12, 14, 28–33].

Finally, we found that ≥ 80% of respondents prescribed probiotics during or after treatment with rifaximin, and significantly more GPs than GEs reported using probiotics during treatment with rifaximin, rather than after the antibiotic. Theoretically, probiotics should be used after rifaximin. Indeed, administration of a probiotic (i.e., a live microorganism that, when administered in adequate amounts, confers a health benefit on the host) together with an antibiotic could be counterproductive, unless bacteria are resistant to the antibiotic in question. This is the case of *Bifidobacterium longum* W11 [46], which displays a nontransmissible antibiotic resistance, due to a nucleotide polymorphism mutation in the rpoB gene, making it resistant to antibiotics of the rifamycin group, including rifaximin [47]. Administration of this probiotic with rifaximin to patients with SUDD resulted in better symptom improvement (particularly stool consistency) compared to that seen with the antibiotic alone [48]. The report was, however, a retrospective one, with the intrinsic bias related to these types of studies.

The theoretical rationale for the use of probiotics in DD is based on several of their properties, such as the ability to maintain adequate bacterial colonisation, to produce an antimicrobial substance (e.g., clausin and reuterin), to compete metabolically with pro-inflammatory organisms, to inhibit adherence and translocation for different pathogen, overall increasing therefore both the anti-inflammatory effects and the capability to enhance anti-infection defences [2, 49–51]. However, current findings do not allow any evidence-based definite conclusion, and as a consequence, there is insufficient data to recommend probiotics in diverticular disease [3, 51, 52].

Our results clearly show some differences in treatment strategies between GEs and GPs, as a gap exists between expert guidance (i.e., national and international guidelines) and the clinical practice of GPs. A probable reason is a not adequate collaboration between GEs and GPs, which may likely result in the drawing-up of guidelines not sufficiently reflecting the reality that GPs face every day, along with their requirements and needs. Unexpectedly, the multivariable analysis did not identify age and/or professional experience (i.e., years of profession) as predictive factors for prescribing or not rifaximin, with the exception of setting 4, where there was a barely positive association for age of respondents as shown by the CIs (OR: 1.02; 95% CI: 1.00 to 1.04). However, as already mentioned before, this study was not conceived to discover the rationale behind the physicians' prescription [53].

Our study has some limitations. Firstly, although surveys of physicians have a long history of use as a cost-effective means to evaluate the physician's prescribed comportment theoretically [54], they can have several drawbacks such as sampling error, non-response error, respondent motivation, availability, and willingness [53, 55]. Bias on self-reported data can also affect a survey: it occurs when individuals offer self-assessed measures of some phenomenon [55]. There can be several reasons physicians could offer biased responses of self-assessed behaviour, ranging from a misunderstanding of questions to social-desirability bias, where the respondent wants to 'look good' in the survey, even if the survey is anonymous [55]. However, surveys have already been performed by other national scientific societies to get a glimpse into physicians' prescription potential behaviour [56, 57]. Secondly, the clinical settings evaluated in this study are multifaceted and might not be consistently well defined in real clinical practice, generating, therefore, a distortion in the answers obtained. Thirdly, the interpretation of the data must be cautious as 60% of the respondents came from the north of the country, suggesting that the results (despite the multivariate analysis) might not be translated to the entire Italian territory.

Fourthly, the use of mesalazine, as well as any information regarding diet (an important factor for the development of diverticula [2]), was not assessed, being not among the aims of the survey. Fifthly, it must be emphasized that the level of evidence that led experts to recommend the use of rifaximin with fibre in clinical settings 2 and 3 was moderate and low, respectively, and all the studies evaluated for these recommendations were performed ≥ 10 years ago, with only a few new studies published recently [17, 58]. Therefore, large and robust clinical trials are demanded.

In conclusion, our results highlight that a reappraisal of (and teaching on) the use of rifaximin in patients with diverticulosis and DD is needed to improve its management, reduce the gap between the evidence available and the daily clinical practice, and optimize, therefore, the use of healthcare resources.

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## Declarations

**Conflict of interest** LG, MB, WM, AC, AG, CL, PUS, PB, FM, RM, SS, and MS: The authors declare that they have no conflict of interest. CS: member of the International Advisory Board and of the Speakers' Bureau of Alfasigma. RV: received a grant from Alfasigma.

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