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Unmet needs in treatment of symptomatic uncomplicated diverticular disease and prevention of recurrent acute diverticulitis: a scoping review

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Abstract

Background: Diverticular disease (DD) represents a common gastrointestinal condition that poses a heavy burden on healthcare systems worldwide. A high degree of uncertainty surrounds the therapeutic approaches for the control of symptoms in patients with symptomatic uncomplicated diverticular disease (SUDD) and primary and secondary prevention of diverticulitis and its consequences.

Objectives: To review the current knowledge and discuss the unmet needs regarding the management of SUDD and the prevention of acute diverticulitis.

Eligibility criteria: Randomized trials, observational studies, and systematic reviews on lifestyle/dietary interventions and medical treatment (rifaximin, mesalazine, and probiotics) of SUDD or prevention of acute diverticulitis.

Sources of evidence: The literature search was performed from inception to April 2023, without language restriction, following the modified Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) reporting guidelines. References of the papers selected were checked to identify additional papers of potential interest. The final list of references was evaluated by a panel of experts, who were asked to check for any lack of relevant studies.

Charting methods: Information on patient population, study design, intervention, control group, duration of the observation, and outcomes assessed was collected by two authors independently.

Results: The review shows a high degree of uncertainty about therapeutic interventions, both dietary/lifestyle and pharmacological, in patients with SUDD, because of the scarcity and weakness of existing evidence. Available studies are generally of low quality, heterogeneous, and outdated, precluding the possibility to draw robust conclusions. Similarly, acute diverticulitis prevention has been seldom investigated, and there is a substantial lack of evidence supporting the role of dietary/lifestyle or pharmacological approaches to reduce the risk of diverticulitis.

Conclusion: The lack of robust evidence regarding therapeutic options for gastrointestinal symptoms in SUDD patients and for primary and secondary prevention of acute diverticulitis remains an important unmet need in the management of DD.

Keywords: diverticulitis, lifestyle intervention, mesalazine, probiotics, rifaximin, symptomatic uncomplicated diverticular disease

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Introduction

Colonic diverticulosis represents one of the most frequent findings during colonoscopy[1] and diverticular disease (DD) represents a common gastrointestinal condition that poses a heavy burden on healthcare systems worldwide.[2] Over 50% of people over the age of 60 and over 60% of people over age 80 have colonic diverticula.[1,3,4]

DD encompasses several clinical scenarios, ranging from asymptomatic diverticulosis to symptomatic uncomplicated or complicated DD (i.e. acute diverticulitis or diverticular bleeding).[5] Although most subjects with DD remain asymptomatic for life (diverticulosis), approximately 15% experience chronic, recurrent gastrointestinal symptoms (e.g. abdominal pain and/or discomfort, alteration of bowel movements, and bloating in the absence of macroscopic signs of colonic inflammation), a condition termed as symptomatic uncomplicated diverticular disease (SUDD) that may be difficult to differentiate from irritable bowel syndrome (IBS). In fact, it is a matter of debate whether SUDD could be considered a disease of its own or whether it represents the coexistence of IBS in patients with colonic diverticula. However, the high prevalence of this condition and the significant impact on quality of life require therapies for the relief of chronic symptoms.[6,7] About 1–4% of DD patients developed acute diverticulitis (e.g. acute symptoms/signs as fever, acute abdominal pain, and leukocytosis) in its uncomplicated or complicated form (with the presence of abscesses, perforation, fistulas, stenosis, or peritonitis),[8] that can recur in approximately one-third of patients.[1,8–11]

Despite the clinical relevance, the high prevalence of DD, and its impact on quality of life, a high degree of uncertainty surrounds the therapeutic approaches for gastrointestinal (GI) symptoms in patients with SUDD and primary and secondary prevention of diverticulitis and its consequences.

This scoping review of the literature aims to summarize the current knowledge and discuss the unmet needs regarding the management of SUDD and the prevention of acute diverticulitis.

Methods

An expert panel composed of six gastroenterologists with long-lasting experience in DD was involved in the identification of the major open questions regarding the medical management of DD. In a face-to-face meeting, chaired by a panel moderator experienced in facilitating group discussions and criteria development, the experts were asked to generate relevant clinical questions using the Patients-Interventions-Comparators-Outcomes (PICO) format (Table 1). Based on the PICO questions identified, a detailed and broad literature search was performed from inception to 12 April 2023, without language restriction, following the modified Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) reporting guidelines[12] (Supplemental Table 1). Studies selected included randomized clinical trials (RCTs) and observational studies assessing the role of lifestyle interventions or medical treatment, that is, rifaximin and mesalazine (often prescribed in patients with SUDD or with a previous episode of diverticulitis, even if not approved in any jurisdiction), and probiotics. When available, results of meta-analyses or systematic reviews were utilized as the primary source of information/data. References of the papers selected were also checked to identify additional papers of potential interest. The final list of references was also evaluated by the panel experts, who were asked to check for any lack of relevant studies. Discordance regarding the pertinence of the study to address each PICO was resolved in a face-to-face meeting.

For eligible studies, information on patient population, study design, intervention, control group, duration of treatment and follow-up, and outcomes assessed was collected by two authors independently. Study characteristics are summarized in tables; no formal quantitative synthesis of results was performed.

Results

Four major questions regarding the management of DD were identified (Table 1). The literature search initially identified 361 papers, of which 62 were considered pertinent to address the PICO questions.

Dietary and lifestyle interventions in patients with SUDD without previous diverticulitis

Two systematic reviews have investigated the role of fibers in SUDD. A systematic review published in 2017[13] included 19 studies: 9 regarding the intake of dietary fibers and 10 with

Table 1. PICO questions identified by the expert panel.

Question	Population	Intervention	Control	Outcomes
Question #1	Patients with SUDD, without a history of diverticulitis	Dietary/lifestyle interventions: 1. High-fiber diet/fiber supplementation 2. Lifestyle intervention (smoking cessation, physical activity, alcohol consumption, weight management).	1. Free diet 2. No lifestyle intervention	Symptoms Diverticulitis Bleeding Quality of life Hospitalizations Need for surgical intervention Resource utilization
Question #2	Patients with SUDD, without a history of diverticulitis	Medical treatment: 1. Rifaximin 2. Mesalazine 3. Probiotics	Placebo Usual practice Head-to-head comparison	Symptoms Diverticulitis Bleeding Quality of life Hospitalizations Need for surgical intervention Resource utilization
Question #3	Patients with a history of diverticulitis	Dietary/lifestyle interventions: 1. High-fiber diet/fiber supplementation 2. Lifestyle intervention (smoking cessation, physical activity, alcohol consumption, weight management).	Placebo Usual practice Head-to-head comparison	Relapse of diverticulitis Symptoms Bleeding Quality of life Hospitalizations Need for surgical intervention Resource utilization
Question #4	Patients with history of diverticulitis	Medical treatment: 1. Rifaximin 2. Mesalazine 3. Probiotics	Placebo Usual practice Head-to-head comparison	Relapse of diverticulitis Symptoms Bleeding Quality of life Hospitalizations Need for surgical intervention Resource utilization

PICO, Patients-Interventions-Comparators-Outcomes; SUDD, symptomatic uncomplicated diverticular disease.

fiber supplementation. Individual studies suggested that fibers, both dietary and supplemental, may provide a benefit in SUDD, but the quality of the studies was very low, with only one study having an optimal score according to the Jadad scale.

As for studies on dietary fibers, only one trial was double-blind, therapeutic regimens were heterogeneous (i.e. dietary fibers, crispbread, high residue, low sugar with unprocessed bran), the amount of dietary fiber utilized was variable (from 20 to 96 g/day), and control groups were also heterogeneous (i.e. symbiotic preparations, rifaximin, lactulose, not high-fiber diet). The follow-up ranged from 3 to 65 months.

Among studies on fiber supplementation, the kind of supplementation was heterogeneous (glucomannan, ispaghula, bran, plantago ovata, and methylcellulose). None of the studies achieved a high dosage of fiber intake with the prescribed supplementation regimen. Control groups were also highly variable, including, among others, the combination of fibers with rifaximin, placebo, and lactulose. The follow-up ranged between 1 and 12 months. The presence of substantial methodological limitations, the heterogeneity of the

Table 2. Systematic reviews on the role of fibers in SUDD.

Author year (ref.)	No. studies/ patients	Type of diverticular disease	Type of studies	Control group	Outcomes	Efficacy
Carabotti, 2017[13]	19/2443	SUDD	DB RCT, RCT, interventional not controlled and observational	Placebo, symbiotic, rifaximin, lactulose, non-high-fiber diet, diet with standard content of fiber, bulk laxative plus antispasmodic	Reduction of abdominal symptoms Occurrence of diverticulitis	The presence of substantial methodological limitations, the heterogeneity of the therapeutic regimens employed, and the lack of *ad hoc* designed studies, did not permit a summary of the outcome measures.
Eberhardt, 2019[14]	Nine, of which seven testing dietary fibers and four included in the meta-analyses	AS or SUDD in older adults	One DB RCT, three DB cross-over RCT, three pre-post-trials (not included in the meta-analysis)	Placebo	Prevention of diverticulitis Stool weight Symptoms Stool transit time	• Prevention of diverticulitis: only one single-arm study. Meta-analysis not feasible • Stool weight: significant increase *versus* placebo [MD: 29 g/day (95% CI: 8–51 g); I^2: 65%; $n=3$ intervention groups (2 ispaghula husk; $n=1$ bran); $n=2$ studies, $n=134$ participants]. • Symptoms: no significant difference *versus* placebo [SMD: −0.13 (95%: −0.31 to 0.05); $p=0.16$; I^2: 33%; $n=4$ intervention groups; $n=161$ participants]. • Stool transit time: no significant difference *versus* placebo [MD: −3.70 (95% CI: −11.06 to 3.65); $p=0.32$; I^2: 0%; $n=3$ intervention groups; $n=134$ participants].

AS, asymptomatic diverticular disease; CI, confidence interval; DB, double-blind; MD, mean difference; RCT, randomized clinical trial; SMD, standardized mean difference; SUDD, symptomatic uncomplicated diverticular disease.

therapeutic regimens, the heterogeneity of treatment in the control groups, and the lack of *ad hoc* designed studies did not allow to draw any conclusion on the potential benefit of dietary or supplemental fibers in patients with SUDD (Table 2).

In 2019, another systematic review summarized the evidence on the effects of dietary fiber modifications, with or without the probiotics use, on the incidence of asymptomatic or SUDD in older adults, as well as on gastrointestinal function and symptoms.[14] Nine studies were included: seven investigated the effect of dietary fibers and two the effect of symbiotics. Only one study, with a high risk of bias, measured the effect of dietary fiber on the incidence of diverticulitis. The mean sample age ranged between 57 and 70 years, and three meta-analyses on different outcomes were performed. Dietary fiber supplementation improved stool weight [mean difference (MD): 29 g/day, $p < 0.00001$; level of evidence: low] but had no significant effect on gastrointestinal symptoms [standardized mean difference (SMD): −0.13, $p=0.16$; level of evidence: low] and stool transit time (MD: −3.70 h, $p=0.32$; level of evidence: low). According to the authors, fibers may have a role in improving bowel function, but future studies are needed to assess their role in preventing diverticulitis. However, in this systematic review, only one meta-analysis addressed our selected outcome (effect on gastrointestinal symptoms).

No additional studies following the publication of the two systematic reviews were identified, nor were studies on lifestyle interventions. The lack of intervention studies evaluating the effects of smoking cessation or body weight reduction/physical activity promotion on DD certainly falls among the unmet needs linked to the management of SUDD. In fact, although

Table 3. Epidemiological studies investigating the role of lifestyle on the risk of DD.

Author (year) (ref.)	Study design	Number of participants	Risk factors evaluated	Results
Strate *et al.*, 2017[15]	Prospective	46,295 men	• Western dietary pattern (high in red meat, refined grains, and high-fat dairy); • Conservative dietary pattern (high in fruits, vegetables, and whole grains)	Men in the highest quintile of the Western Dietary Pattern score had a 55% higher risk of diverticulitis (HR = 1.55; 95% CI: 1.20–1.99).
Aune *et al.*, 2020[16]	Meta-analysis of five prospective studies	865,829	• Dietary fiber intake	The risk of DD was reduced by 26% for every 10 g/day of dietary fiber (RR = 0.74; 95% CI: 0.71–0.78). A risk reduction of 23%, 41%, and 58% was documented for an intake of 20, 30, and 40 g/day, respectively, compared to 7.5 g/day.
Aune *et al.*, 2017[17]	Meta-analysis of five prospective studies	147,869	• Physical activity	The risk of DD was 24% lower for high levels of physical activity compared to low levels (RR = 0.76; 95% CI: 0.63–0.93) and 26% lower for highly vigorous *versus* low levels of vigor physical activity (RR = 0.74; 95% CI: 0.57–0.97).
Aune *et al.*, 2017[17]	Meta-analysis of six prospective studies	1,636,777	• BMI	An increase in BMI of 5 units was associated with an excess risk of DD of 28% (RR = 1.28; 95% CI: 1.18–1.40), an excess risk of diverticulitis of 31% (RR = 1.31; 95% CI: 1.09–1.56), and an excess risk of complications of DD of 20% (RR = 1.20; 95% CI: 1.04–1.40). The risk of DD increased linearly with BMI, being three times greater for subjects with a BMI of 40 or more compared to subjects with a BMI of 20 (RR = 3.01; 95% CI: 2.06–4.39).
Aune *et al.*, 2017[18]	Meta-analysis of five prospective studies	385,291	• Smoking	The risk of incident DD was 36% higher in current smokers (RR = 1.36; 95% CI: 1.15–1.61) and 17% higher for former smokers (RR = 1.17; 95% CI: 1.05–1.31). The risk increased by 11% for every 10 cigarettes smoked during the day.
Liu *et al.*, 2017[19]	Prospective	51,529 men	• Low-risk lifestyle defined as average red meat intake $<$51 g/day, dietary fiber intake in the highest 40% of the cohort (approximately 23 g/day), vigorous physical activity in the highest 50% of the cohort participants with a non-zero value (approximately 2 h of exercise per week), normal BMI between 18.5 and 24.9 kg/m^2 and never smoker.	Compared to men with no low-risk lifestyle factors, the multivariable relative risks of diverticulitis were 0.71 (95% CI: 0.59–0.87) for men with one low-risk lifestyle factor; 0.66 (95% CI: 0.55–0.81) for two low-risk factors; 0.50 (95% CI: 0.40–0.62) for three low-risk factors; 0.47 (95% CI: 0.35–0.62) for four low-risk factors; and 0.27 (95% CI: 0.15–0.48) for five low-risk factors. Based on data from these studies, adhering to a low-risk lifestyle could prevent 50% (95% CI: 20–71%) of incident diverticulitis cases.

BMI, Body Mass Index; CI, confidence interval; DD, diverticular disease; HR, Hazard Ratio; RR, Relative Risk.

epidemiological studies suggest an important protective role of lifestyle habits on the risk of DD (Table 3),[15–19] no study conducted on SUDD patients is available.

Overall, epidemiological studies indirectly provide a rationale for assessing the efficacy of lifestyle interventions to prevent DD complications even in SUDD patients.

Medical treatment in patients with SUDD, without previous diverticulitis

Rifaximin. It has been proposed that gut microbiota imbalance is one of the pathogenetic mechanisms underlining symptomatic DD. On this basis, rifaximin, a broad-spectrum non-absorbable antibiotic, has been tested as a possible treatment for symptoms relief in DD.[20]

In a systematic review, Maconi *et al.*[21] examined the evidence regarding the role of medical therapy in reducing symptoms and preventing acute diverticulitis. Overall, 31 prospective clinical studies were analyzed, which presented high heterogeneity in the study design, inclusion criteria, patient characteristics, treatment regimens, and combinations and outcome type. This heterogeneity precluded quantitative synthesis of the results, limiting their interpretation. However, in all nine randomized trials that included symptom reduction as an outcome, a dose of 400 mg/12 h of rifaximin was able to reduce lower GI symptoms. Furthermore, cumulative data from the four randomized trials evaluating the prevention of acute diverticulitis demonstrated a significant benefit with rifaximin plus fiber compared to fiber alone [1-year acute diverticulitis rate: 11/970 (1.1%) *versus* 20/690 (2.9%); ($p = 0.012$)], with a number needed to treat (NNT) of 57 to prevent an attack of acute diverticulitis.

A meta-analysis of four RCTs for a total of 1660 patients compared the long-term efficacy of rifaximin plus fiber supplementation administration compared with supplementation alone.[22] The study documented a pooled risk difference (RD) for symptom reduction of 29.0% [rifaximin *versus* control; 95% confidence interval (CI): 24.5–33.6%; $p < 0.0001$] with an NNT of 3. Furthermore, there was an RD for the complication rate of −1.7% in favor of rifaximin (95% CI: −3.2 to −0.1%; $p = 0.03$; NNT = 59).

The only double-blind placebo-controlled trial included 168 SUDD outpatients who were treated with cyclic (i) fiber supplementation (glucomannan 2 g/day) plus rifaximin 400 mg b.d. for 1 week per month ($n = 84$) or (ii) glucomannan 2 g/day plus placebo two tablets b.d. for 1 week per month ($n = 84$).[23] After 1 year, patients treated with rifaximin were significantly more asymptomatic or mildly symptomatic compared to the placebo group (68.9% *versus* 39.5%, $p = 0.001$). The GI symptoms that were mainly influenced by rifaximin treatment were bloating and abdominal pain or discomfort ($p < 0.001$).

In addition to RCTs, the effectiveness of rifaximin in the treatment of SUDD has been investigated in several observational studies.

Table 4 reports the main characteristics of experimental[23–30] and observational[31–34] studies on rifaximin in patients with SUDD.

Data arising from non-randomized studies, despite the lack of a control group or the likelihood of selection bias, thus representing a weakness in the quality of this evidence, are in line with the conclusions of RCTs. In this respect, the application of propensity score methods could reduce the risk of bias due to the non-comparability of baseline characteristics and disease severity of patients treated with rifaximin or alternative approaches. In summary, RCTs and observational studies suggest a benefit of rifaximin associated with fiber in reducing lower GI symptoms associated with SUDD. However, the paucity of data and the lack of recent RCTs do not allow us to reach strong conclusions.

Mesalazine. Mesalazine has been proposed as a treatment for low-grade inflammation of the colonic mucosa in SUDD. To date, three meta-analyses of randomized controlled trials (RCTs) on mesalazine treatment have been published,[35–37] one of which included only studies in patients with previous diverticulitis.[35]

The meta-analysis by Iannone *et al.*[36] included both studies on SUDD and studies on acute uncomplicated diverticulitis. Regarding SUDD, only one RCT (123 patients) evaluated the remission of symptoms using mesalazine (3000 mg/day for 6 weeks) *versus* placebo, without showing a benefit for mesalazine use [odds

Table 4. Main characteristics of studies investigating the role of rifaximin in SUDD.

Author year (ref)	No. patients	Type of diverticular disease	Study type/ No. arms	Intervention	Control	Follow-up	Outcome	Efficacy
Comparato *et al.*, 2007[24]	58	SUDD	RCT/2	Rifaximin for 10 days every month for a period of 6 months	Mesalazine for 10 days every month for a period of 6 months	6 months	GSS	Both groups showed a highly significant reduction of their mean GSS; treatment with mesalazine showed better results than rifaximin in diminishing mean GSS ($p = 0.019$)
Colecchia *et al.*, 2007[25]	307	SUDD	RCT/2	Rifaximin (400 mg bid for 7 days every month) plus dietary fiber supplementation (at least 20 g/day)	Dietary fiber supplementation alone.	24 months	Symptoms score Remission	Significant difference ($p < 0.01$) in favor of Rifaximin group in symptoms score Probability of symptom remission significantly higher ($p < 0.0001$) in the Rifaximin group
Comparato, 2007[26]	268	SUDD	RCT/4	Rifaximin (200 mg bid) (R1)	Rifaximin (400 mg bid) (R2) Mesalazine (400 mg bid) (M1) Mesalazine (800 mg bid) (M2)	12 months	12 symptoms GSS	R2, M1, and M2 were effective in reducing tenesmus, bloating, diarrhea, well-being, and bleeding after 6 months and lower abdominal pain, tenesmus, bloating, diarrhea, well-being, and bleeding after 12 months of therapy. Patients treated with mesalazine (Groups M1 + M2) had a lower GSS than subjects treated with rifaximin (Groups R1 + R2) during the 12-month follow-up period.
D'Incà *et al.*, 2007[27]	64	SUDD	DB RCT/2	bran (20 g/ day) + rifaximin (1200 mg/day) for 14 days	Bran (20 g/ day) + placebo for 14 days	14 days	Seven symptoms GSS	Significant reduction of constipation, abdominal pain, and bloating in the active group; in the placebo group, improvement was observed only in straining. The GSS significantly reduced after rifaximin, while it remained practically unchanged after placebo
Di Mario *et al.*, 2005[28]	170	SUDD	RCT/4	Rifaximin (200 mg bid) (R1)	Rifaximin (400 mg bid) (R2) Mesalazine (400 mg bid) (M1) Mesalazine (800 mg bid) (M2)	3 months	11 symptoms GSS	R2, M1, and M2 were effective in reducing lower abdominal pain/discomfort, tenesmus, and diarrhea. All groups but Group R1 had a significantly reduced GSS. No statistically significant differences were noted among the three effective therapies, although all of them were better than the Group R1 treatment in diminishing such score. Patients treated with mesalazine (Groups M1 + M2) had a lower GSS than subjects treated with rifaximin (Groups R1 + R2)
Latella, 2003[29]	968	SUDD	RCT/2	Fiber supplementation with 4 g/day glucomannan plus 400 mg rifaximin twice daily for 7 days every month	Fiber supplementation with 4 g/day glucomannan	12 months	Six symptoms GSS	Frequency and severity of symptoms significantly lower in the group treated with glucomannan plus rifaximin. Patients treated with rifaximin showed a more marked reduction in the GSS at 4, 8, and 12 months than those treated with glucomannan only.
Papi *et al.*, 1995[23]	168	SUDD	DB RCT/2	Fiber supplementation with 2 g/day glucomannan plus 400 mg rifaximin twice daily for 7 days every month	Fiber supplementation with 2 g/day glucomannan plus placebo for 7 days every month	12 months	Six symptoms GSS	Rifaximin group showed a significant reduction in the GSS as compared to placebo at 6, 9, and 12 months. After 12 months of treatment, 68.9% of patients in the rifaximin group were symptom-free or mildly symptomatic, as compared to 39.5% in the placebo group ($p = 0.001$)

(Continued)

Table 4. (Continued)

Author year (ref)	No. patients	Type of diverticular disease	Study type/ No. arms	Intervention	Control	Follow-up	Outcome	Efficacy
Papi *et al.*, 1992[30]	217	SUDD	RCT/2	Fiber supplementation with glucomannan plus 400 mg rifaximin twice daily for 7 days every month	Fiber supplementation with glucomannan	12 months	Eight symptoms GSS	Patients treated with glucomannan plus rifaximin showed a 63.9% reduction of the score as compared to 47.6% in patients treated with glucomannan only ($p < 0.001$).
De Bastiani *et al.*, 2021[31]	286	SUDD	Observational retrospective/1	Rifaximin 400 mg b.i.d. for 5, 7, or 10 days monthly, up to 3 months		3 months	Four symptoms (abdominal pain, swelling, constipation, and diarrhea) were assessed with a VAS scale	After 3 months, a significant reduction in VAS score was observed in all symptoms assessed. The proportion of patients with at least one symptom decreased from 91.6% at baseline to 73.8% after 3 months. Acute diverticulitis occurred in nine (3.1%) patients.
Di Mario *et al.*, 2019[32]	816	SUDD	Observational retrospective/2	Rifaximin 800 mg/day for 7 days every month (Group A, $N = 346$)	Any other treatment on demand (Group B, $N = 470$)	8 years	Two symptoms (left lower abdominal pain and bloating) assessed by a VAS	Median (IQR) VAS score for pain at the 8-year follow-up was 3 (3–4) and 6 (5–7), in Group A and B, respectively ($p < 0.000$). Both bloating and daily bowel movements were significantly reduced in Group A. Acute diverticulitis occurred in nine (2.6%) patients in Group A and 21 (4.5%) patients in Group B ($p = 0.155$). Surgery occurred in four (1.2%) patients in Group A and nine (1.9%) in Group B ($p = 0.43$). Disease-related mortality occurred in no patient in Group A and 2 (0.4%) patients in Group B ($p = 0.24$).
Moniuszko and Rydzewska, 2017[33]	142	SUDD and mild diverticulitis	Observational retrospective/1	Three cycles of rifaximin at a dose of 2×400 mg daily for 7 days over 3 consecutive months		3 months	The severity of symptoms on a 0–3 scale	After one cycle of therapy, the mean intensity of symptoms decreased from 1.7 ± 0.7 to 0.8 ± 0.3 points. After three cycles, the severity of symptoms decreased to an average of 0.3 ± 0.1, and 75% of patients reported no abdominal pain.
Stallinger *et al.*, 2014[34]	1003	SUDD	Observational prospective/1	Rifaximin 400 mg b.i.d. for 7–10 days, followed by a 3-week treatment break		3 months	Six symptoms GSS	A statistically significant symptom reduction was documented for all symptoms. At the end of follow-up, >90% of the patients reported only mild or no symptoms except for flatulence (88%). Total symptom scores decreased from 7.2 ± 2.7 at baseline to 1.5 ± 1.6 at the final visit ($p < 0.001$).

DB, double-blind; GSS, Global symptomatic score; IQR, Interquartile Range; RCT, randomized clinical trial; SUDD, symptomatic uncomplicated diverticular disease; VAS, Visual Analogue Scale.

ratio (OR): 1.04; 95% CI: 0.8–1.34].[38] As for symptomatic relapses, two RCTs conducted in SUDD patients were identified, for a total of 216 patients.[39,40] Treatment with mesalazine (1600 mg/day for 12 months) was associated with a significant reduction (48%) in the risk of symptomatic relapse (OR: 0.52; 95% CI: 0.28–0.97). There was a reduction in diverticula-related symptoms with mesalazine compared to control interventions (placebo, rifaximin, or *Lactobacillus casei* sub-species DG) in four of six studies of symptomatic uncomplicated DD.[24,26,38–41] In the analysis of two studies of SUDD patients reporting a global symptom score,[24,26] a lower mean score was found with mesalazine (800 or 1600 mg/day for 10 days/month for 6–12 months) compared to control interventions at maximum follow-up (2 studies, 326 participants, SMD = −1.01, 95% CI: −1.51 to −0.52). However, the global symptom score included also upper GI symptoms, thus reducing the clarity of these results.

In the meta-analysis by Picchio *et al.*[37] RCTs comparing mesalazine *versus* placebo in patients with SUDD were included. Four RCTs enrolled 379 patients, 197 treated with Mesalazine and 182 with placebo. Three studies provided data on symptom relief,[38,40,41] that was achieved in 97/121 (80.0%) patients in the mesalazine group and 81/129 (62.7%) patients in the placebo group (OR: 0.43; 95% CI: 0.24–0.75; $p = 0.003$ in favor of mesalazine group). Two studies provided information on the occurrence of diverticulitis during follow-up,[40,42] which occurred in 23/119 (19.3%) patients in the mesalazine group and 34/102 (33.3%) patients in the placebo group (OR: 0.35; 95% CI: 0.17–0.70; $p = 0.003$ in favor of the mesalazine group).

Summary characteristics of RCTs assessing the effect of mesalazine on symptoms in patients with SUDD are reported in Supplemental Table 2.

In summary, existing evidence, particularly evidence deriving from placebo-controlled RCTs, suggests that mesalazine can play a role in reducing symptoms. However, the total number of studies and patients involved is small, thus precluding the possibility of solid conclusions.

No studies were identified following the publication of the two meta-analyses in 2018.

Probiotics. A systematic review evaluated the effectiveness of probiotics in SUDD in terms of abdominal symptoms remission and acute diverticulitis prevention.[43] Eleven studies were identified: two were double-blind placebo-controlled RCTs, five were open-label RCTs, and the remaining three were non-randomized open-label studies. Three studies included patients with symptomatic uncomplicated disease, whereas four studies included patients with symptomatic uncomplicated disease in remission. The remaining four studies examined patients with complicated or acute diverticulitis. Mainly single probiotic strains were used (72.7%), most frequently Lactobacilli. Follow-up ranged from 1 to 24 months. The interventions were variable: in eight studies, the probiotic was administered together with antibiotics or anti-inflammatory drugs and compared with the effectiveness of the drug alone; in three studies, the probiotic was compared with a diet rich in fiber or used together with phytoextracts. As an outcome measure, four studies evaluated the rate of acute diverticulitis occurrence, six studies the abdominal symptoms reduction, and six studies the abdominal symptoms recurrence. Meta-analysis on the efficacy of the probiotics in DD was not performed due to the poor quality of available studies. In the only double-blind, placebo-controlled RCT[40] on patients with SUDD, 210 patients were randomized into 4 groups: (A) Mesalazine + placebo; (B) lactobacillus + placebo; (C) mesalazine + lactobacillus; (D) placebo + placebo. Treatments with cyclic Mesalazine and *Lactobacillus casei* subsp DG, particularly if administered in combination, appeared to be better than placebo for maintaining remission of uncomplicated symptomatic diverticular disease at 12 months (relapse in 0% of cases in group C, 13.7% in group A, 14.5% in group B, and 46% in group D).

In addition, a further double-blind placebo-controlled RCT not included in the previous systematic review, included 120 SUDD patients treated for 3 months with (i) supplementation of *Lactobacillus rhamnosus, Enterococcus faecium, Lactobacillus acidophilus*, and *Lactobacillus plantarum* (1 ml/kg/day) or (ii) placebo.[44] Alteration of bowel habits (constipation, diarrhea), mucorrhea, and back pain were significantly reduced in patients supplemented with probiotics, but the reduction of abdominal pain was similar between groups.

A reduction in abdominal swelling and pain in subjects with SUDD is associated with the use of *L. acidophilus*, *Lactobacillus helveticus*, and *Bifidobacterium* spp. 420 or *Lactobacillus paracasei* has been documented in non-randomized studies[45] or small RCTs.[46,47]

Overall, the evidence supporting the role of probiotics in SUDD is based on small, heterogeneous studies, of generally poor methodological quality. Furthermore, existing studies were mainly focused on symptoms, and there is a substantial lack of information regarding the possible role of probiotics in reducing the risk of diverticulitis.

Dietary and lifestyle interventions in patients with previous diverticulitis with or without GI symptoms

Evidence regarding the role of fiber intake in preventing the recurrence of diverticulitis is scant.

In 2018, a systematic review identified three studies in which dietary fiber intake was modified after an acute episode of uncomplicated diverticulitis.[48] Although all three studies reported data on symptoms and two out of three on diverticulitis relapses, the absence in two studies of a control group taking a low-fiber diet precluded the possibility of performing a meta-analysis. Furthermore, one of the randomized trials considered[49] compared fiber supplement *versus* fiber supplement + rifaximin, precluding the unbiased assessment of the role of fiber supplementation. Overall, the strength of evidence for the possible role of fiber in preventing recurrence was considered by the authors as 'very low'.

No additional, more recent studies were identified. No lifestyle intervention studies for the prevention of recurrence of diverticulitis (type of diet, BMI, physical activity, smoking) were identified. However, we can assume that the beneficial effect of dietary fiber and lifestyle intervention reported in observational studies in patients without previous diverticulitis [increase in physical activity, weight loss in case of overweight or obesity, smoking cessation, avoiding Non-Steroidal Anti-Inflammatory Drug (NSAIDs)] can be successfully applied to patients who have had acute diverticulitis to reduce diverticulitis recurrence.

Medical treatment in patients with previous diverticulitis with or without GI symptoms

Rifaximin. The role of rifaximin in the prevention of recurrent diverticulitis has been evaluated in a few studies, most of them non-randomized. In a multicenter, randomized open-label study conducted on 165 patients with a recent diagnosis of acute diverticulitis, the combination of rifaximin (400 mg twice a day for 7 days a month) and fibers (3.5 g/day) was demonstrated to be more effective than fibers alone in preventing recurrence at 48 weeks (10.4% *versus* 19.0%).[50] In multivariable analysis, the risk of relapse for the fiber supplement-only group compared with supplement + rifaximin was 2.64 (HR; 95% CI: 1.08–6.46; $p = 0.033$). Regarding gastrointestinal symptoms, no improvements were shown at 48 weeks in either group.

In a retrospective study on patients with a previous acute diverticulitis episode, 72 subjects treated with rifaximin were compared with 52 subjects treated with mesalazine.[51] During a median follow-up of 15 months, the risk of diverticulitis recurrence was 73% lower (HR = 0.27; 95% CI: 0.10–0.72) with rifaximin, administered at a dose of 400 mg twice a day for 10 days per month.

In another controlled, non-randomized study, patients with an acute episode of diverticulitis, once remission was achieved, were treated with mesalazine 1.6 g/day (59 patients) or with rifaximin 800 mg/day for 7 days a month (52 patients).[49] The probability of maintaining clinical remission at 24 months was significantly higher in the mesalazine group ($p = 0.002$).

The paucity of RCTs and the major methodological flaws related to the risk of selection bias in non-randomized studies prevent any clear conclusion regarding the treatments for patients with previous diverticulitis. In this respect, the treatment for the prevention of diverticulitis is crucial, especially in the first 2 years after the acute event because of the greater incidence of recurrence registered in this period. Therefore, in patients with previous diverticulitis, this represents an important unmet need.

Mesalazine. A systematic review by the Cochrane Collaboration published in 2017 included 7 randomized trials (RCTs) with a total of 1805

participants.[52] All seven studies had an uncertain or high risk of bias. The authors found no evidence of an effect when comparing mesalazine *versus* control for the prevention of recurrent diverticulitis (31.3% *versus* 29.8%; RR: 0.69, 95% CI: 0.43–1.09; very low quality of evidence).

In a further meta-analysis by Kahn *et al.*,[35] RCTs comparing the effect of mesalazine *versus* placebo on diverticulitis recurrence in patients with symptomatic DD were included. Six RCTs enrolling a total of 1918 patients were identified. There was no difference in diverticulitis recurrence between mesalazine and placebo groups (OR: 1.20, 95% CI: 0.96–1.50, $p = 0.11$). There was a low level of heterogeneity between studies ($I^2 = 9\%$, $p = 0.36$). When the mesalazine dose was ⩽2 g/day, there was no difference in the relapse rate between the two groups (OR: 1.10, 95% CI: 0.79–1.54, $p = 0.58$). When the mesalazine dose was >2 g/day, the risk of relapse was higher in the mesalazine group (OR: 1.28, 95% CI: 1.02–1.62, $p = 0.04$). The authors concluded that mesalazine does not prevent the recurrence of diverticulitis.

A more recent systematic review summarized the evidence deriving from studies that tested the effectiveness of mesalazine in preventing the recurrence of acute diverticulitis episodes.[53] Authors identified six randomized trials comparing treatment with mesalazine in various doses and schedules of administration *versus* placebo, for a total of 1898 participants. The meta-analysis of the six RCTs found a summary OR of 1.15 (95% CI: 0.92–1.44) for diverticulitis recurrence with mesalazine. No dose–effect relationship was documented. In the same systematic review, four RCTs reported time to relapse, but with conflicting results. Parente *et al.*[54] reported worse outcomes with mesalazine: patients treated with mesalazine 1.6 g/day (10 days per month) had a shorter mean time to relapse than patients treated with placebo [MD, −151 days (95% CI: −366 to −66 days)]. The other three studies found no statistically significant differences between mesalazine and placebo.[38,55]

The role of mesalazine in the prevention of recurrence of diverticulitis was also investigated in a few non-randomized studies.

The two observational studies previously discussed comparing mesalazine *versus* rifaximin[52,53] produced conflicting results.

In another study on 218 patients, the combination of mesalazine and rifaximin (109 patients treated with rifaximin 400 mg bid plus mesalazine 800 mg bid for 7 days, followed by rifaximin 400 mg bid plus mesalazine 800 mg bid for 7 days/month) was shown to be more effective than rifaximin alone (109 patients treated with rifaximin 400 mg bid for 7 days, followed by rifaximin 400 mg bid for 7 days/month) in relieving symptoms (absence of symptoms at 12 months: 86% *versus* 49%; $p < 0.0005$) and in preventing the recurrence of diverticulitis (12-month recurrence rate of 2.8% *versus* 18.0%).[56]

Despite non-randomized studies suggesting a possible benefit of mesalazine in preventing the recurrence of diverticulitis, this is not confirmed by double-blind, placebo-controlled trials. The high risk of selection bias in non-randomized studies represents a major methodological flaw limiting the interpretation of the results.

Probiotics. No studies investigating the role of probiotics in the prevention of diverticulitis recurrence were found. The bibliographic search led to the identification of one potentially pertinent paper. In a pilot study, 30 consecutive patients suffering from uncomplicated diverticulitis were monitored.[57] After achieving remission, patients were randomly assigned to one of the following groups: group A, balsalazide 2.25 g daily for 10 days every month plus VSL#3 450 billion/day for 15 days every month and group B, VSL#3 only 450 billion/day for 15 days each month. Since patients in both groups received the probiotic, no conclusion can be drawn about its efficacy.

Discussion

This scoping review shows a high degree of uncertainty about therapeutic interventions, both lifestyle and pharmacological, in uncomplicated DD patients because of the scarcity and weakness of existing evidence. It is even more surprising, considering the high DD prevalence, its impact on quality of life, and its heavy burden on healthcare systems.

Regarding SUDD, even if a standardized diagnostic criterion is not yet available, chronic abdominal symptoms attributable to diverticula influenced significantly the quality of life. In fact, in an observational multicenter study, it has been shown that the quality of life of SUDD patients is similar to

patients with a previous episode of diverticulitis, likely suggesting that the presence of troublesome recurrent abdominal symptoms is perceived as a full disease similarly to patients who have experienced a diverticular complication.[7]

Unfortunately, as shown in this literature review, since all existing evidence regarding SUDD is of low quality, heterogeneous, and outdated, there are still no clearly agreed therapeutic approaches for improving GI symptoms and preventing acute diverticulitis in this condition. We evaluated the three most common medical treatments utilized in SUDD management such as rifaximin, mesalazine, and probiotics. Particularly, rifaximin associated with fiber appears to be effective in improving GI symptoms (NNT = 3), but a very high NNT (NNT = 57) was found when prevention of acute diverticulitis was considered. However, based on these data, we can conclude that evidence supporting the use of rifaximin for the primary prevention of acute diverticulitis is scarce and probably not cost-effective. In fact, the only RCT showing a positive effect is now dated and no longer replicated. With regard to mesalazine, non-randomized studies suggest a possible benefit of mesalazine in both outcomes considered, but substantial methodological flaws limit the interpretation of the results. On the other hand, the evidence supporting the role of probiotics in SUDD similarly has a low and heterogeneous quality of evidence.

Another relevant outcome, acute diverticulitis prevention, has been scarcely studied. This would be an important issue since several epidemiological studies showed increasing acute diverticulitis incidence especially in Western countries.[4,58–61] At now, there are still no shared pharmacologic approaches for primary and secondary prevention of acute diverticulitis. Treatment interventions for reducing the risk of an acute episode are crucial, especially in the first 2 years after the acute event because of the greater incidence of recurrence registered in that period. While for mesalazine the existing literature shows proof of non-efficacy, for rifaximin there is evidence to suggest a hypothetical benefit.[49] Thus, the management of patients with previous diverticulitis is still an important unmet need, as no clear conclusions can be drawn on treatment options in this context, due to the low quality and scarce evidence available.

Evidence suggesting the protective role of dietary and lifestyle factors (i.e. high-fiber diet, smoking cessation, body weight reduction, and physical activity promotion), on the risk of complicated DD comes only from epidemiological studies. Intervention studies assessing lifestyle factors in DD patients, an important area of interest, are currently unavailable. Since studies evaluating the effect of a high-fiber diet on pain reduction are of low quality and heterogeneous, it is not possible to draw a solid conclusion on the potential benefit of dietary or supplementary fiber in SUDD patients. Although there is a lack of intervention studies evaluating the effect of dietary and lifestyles, it is reasonable to believe that they may still be useful suggestions for preventing disease complications. However, the scarcity of solid evidence supporting dietary fiber and the lack of intervention studies evaluating lifestyle habits on DD certainly are among the unmet needs linked to SUDD management.

Other important outcomes still remain completely unexplored, as there is no study attempting to assess the risk of bleeding, the quality of life, the need for surgery, the rate of hospitalization, and resource utilization.

Moreover, considering the attempt to better address therapeutic studies by accurate clinical endoscopic scores, the recent proposal of innovative scores should be mentioned. Particularly, the Diverticular Clinical Score (DICS) a clinical score for SUDD post-acute diverticulitis,[62] and the Combined Overview on Diverticular Assessment (CODA) score that combined both endoscopic and clinical parameters, predict the occurrence of acute diverticulitis and surgery due to diverticular complication.[63] We hope that these scores will be used in the future to verify the effectiveness of the medical treatments.

Therefore, these are crucial fields of interest on which future research should focus.

Conclusion

In summary, the lack of robust evidence regarding therapeutic options for GI symptoms in SUDD patients and prevention of acute diverticulitis remains an important unmet need in the management of DD.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Marilia Carabotti: Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing.

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Availability of data and materials
Data sharing is not applicable.

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