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# Is mesalazine treatment effective in the prevention of diverticulitis? A review

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**Abstract.** **Diverticulitis is the most severe form of Diverticular disease (DD). An effective treatment strategy for its prevention has not yet been defined. This review aimed to provide a viewpoint on the role of mesalazine, also note as 5-aminosalicylic acid (5-ASA), in the prevention of diverticulitis. A systematic electronic search of relevant articles was performed using PubMed, Embase, Scopus, and Cochrane. Randomized controlled trials (RCTs), open trials, and retrospective studies, published between January 1999 and January 2020, were identified. Twelve eligible studies that analyzed primary or secondary outcomes of diverticulitis were included. The population included patients with symptomatic uncomplicated diverticular disease (SUDD), or patients with a history of diverticulitis. All studies compared 5-ASA to placebo, rifaximin, or other treatments. Two studies, including 359 patients, assessed the efficacy of 5-ASA in preventing the first appearance of diverticulitis in patients with SUDD. Of these, one showed that 5-ASA was effective, and one did not. Ten studies, including 2.995 patients, assessed the efficacy of 5-ASA treatment in preventing the recurrence of diverticulitis in patients with a history of diverticulitis. Four studies showed that 5-ASA had a certain degree of efficacy. All four RCTs demonstrated that 5-ASA did not significantly reduce the rate of diverticulitis recurrence. In a retrospective trial, 5-ASA was less effective than rifaximin in preventing diverticulitis recurrence. In an open trial, there was no difference between 5-ASA and probiotic treatment. Overall, there is currently conflicting evidence regarding the efficacy of 5-ASA treatment in the prevention of diverticulitis and further RCTs are needed.**

*Key Words:*
Diverticular disease, Diverticulitis, Diverticulosis, Symptomatic uncomplicated diverticular disease, Mesalazine, Rifaximin.

## Introduction

Diverticulosis of the colon is a common condition that has an increasing incidence in developed countries and is associated with ageing. The prevalence of diverticulosis increases with age; in fact, it develops in more than 50% of octogenarians[1]. It affects men and women equally[1,2]. Physical inactivity, reduced intake of dietary fiber, chronic constipation, obesity, smoking, and treatment with non-steroidal anti-inflammatory drugs, as well as genetic factors, have also been shown to increase the risk of developing diverticula in the colon[1-8]. However, some factors, such as low-fiber diet and constipation, are still uncertain and debated[7]. Several of these factors could be also risk factors for the development of diverticulitis and bleeding[4].

Diverticulosis can occur in any segment of the colon. The sigmoid colon is the most affected in the Western countries' population, while the right colon in the Asian population[9].

Usually, diverticulosis indicates only the presence of diverticula in the colon, and its finding is incidental[1,10]. The term diverticular disease (DD) is used to indicate a more clinically significant disease[1]. Symptomatic uncomplicated DD (SUDD) is a clinical form of DD that is characterised by abdominal pain, bloating, and changes in bowel habit. In SUDD colonic inflammation is absent[10,11]. Segmental colitis associated with diverticulosis (SCAD) is characterised by the presence of a non-specific inflammation of the mucosa surrounding the diverticula[1,9]. It may lead to rectal bleeding, diarrhea, and abdominal pain[12-14]. SCAD prevalence is difficult to establish, as people usually lack the awareness of this condition, and its clinical signs overlap with ulcerative coli-



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tis (UC) or Crohn's disease. Nevertheless, studies reported SCAD prevalence to be 0.25-1.4% in the general population. However, in patients with DD, its prevalence varies between 1.15 and 11.4%[13,14].

Notably, diverticulitis is the most severe form of DD[15]. In the past, diverticulitis was reported to occur in approximately 10-25% of patients with diverticula[1,10,15]. Swanson et al[15] have shown that it occurs in less than 5% of patients with diverticulosis (Figure 1). Diverticulitis is characterised by inflammation of diverticula and micro-perforations of the diverticula wall. It is classified as acute or chronic diverticulitis, and as uncomplicated or complicated diverticulitis (based on the presence of perforations, abscesses, fistulas, and obstructions)[15]. Typically, the symptoms of diverticulitis include abdominal pain, diarrhea, fever, and localised peritonitis. It is also associated with increased inflammatory indices (leukocytes, erythrocyte sedimentation rate, C-reactive protein, and faecal calprotectin). The diagnosis of diverticulitis must be confirmed by intravenous contrast-enhanced computed tomography (CT)[9]. In 2012, the number of hospital admissions for diverticulitis in the United States was 216,560 with a cost of 2.2 billion dollars[10]. In 2010, the mortality rate for diverticulitis without haemorrhage in the United States was 0.3%[10]. The Italian National Institute of Statistics estimated that more than 8 million Italians > 60 years old may have diverticulosis and more than 678 million euros could be spent in the management of this population. On the other hand, for the majority of patients, medical treatment presents no advantage in terms of prevention of the occurrence/recurrence of acute diverticulitis and surgery[16]. In Italy, the rate of hospitalisation for acute diverticulitis steadily increased between 2008 and 2015, due to the hospitalisation of younger individuals, especially men[17,18].

The treatment strategies for the various forms of DD (diverticulosis, SUDD, SCAD, diverticulitis) are different[16]. In patients with asymptomatic diverticulosis, no treatment is indicated, and follow-up is not necessary[1,10]. SUDD can be treated with dietary fibre supplementation and cyclic treatment with rifaximin 800 mg administered daily for seven days per month[1,11,18-22]. SCAD can regress both spontaneously and after treatment with mesalazine (5-aminosalicylic acid: 5-ASA)[12-14]. For a long time, even in the absence of strong evidence, the use of broad-spectrum antibiotics has been suggested for the treatment of patients with acute uncomplicated diverticulitis (AUD). The treatment of CT-confirmed AUD without antibiotics appears to be feasible, safe, and effective[23,24]. Adding broad-spectrum antibiotics to the treatment regimen does not significantly decrease the frequency of recurrence, complications, hospital readmissions, and surgery, compared with non-antibiotic treatment[25-28]. Excluding antibiotic therapy for AUD also appears to be safe in the long run[29]. For AUD patients, the American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis proposes that antibiotic therapy should be used selectively, rather than routinely[30,31].

In current practice, it is common for diverticulosis patients to undergo therapies (dietary regimens, probiotics, rifaximin) to prevent complications (specially diverticulitis), irrespective of the

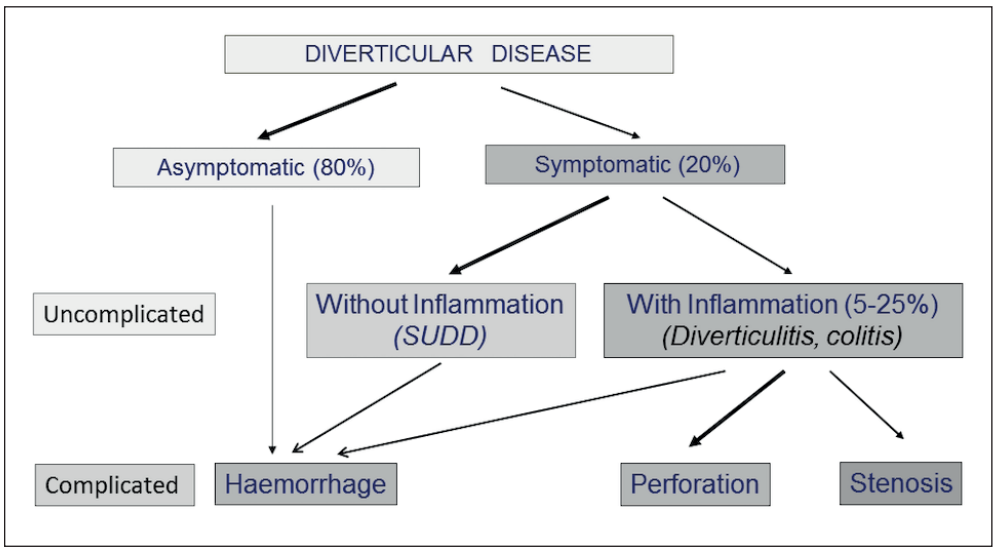


**Figure 1.** Clinical scenarios of diverticular disease of the colon. The range 5-25% of the prevalence of symptomatic diverticular disease with inflammation (diverticulitis and colitis) includes both the data of the oldest studies and those of the more recent studies (for details see the text).

specific entities of the DD (diverticulosis, SUDD, SCAD)[32]. 5-ASA is commonly used for treating patients with SUDD and even patients with diverticulosis[32]. The effectiveness of 5-ASA in preventing diverticulitis remains uncertain[1,10,33-37].

The purpose of this review is to provide a critical viewpoint on the role of 5-ASA in the current management of DD. In particular, we critically evaluated and discussed the role of 5-ASA in the prevention of diverticulitis, analyzing both the original articles, and the systematic reviews, and recent meta-analysis.

## Materials and Methods

The recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analyses Statement were applied to analyse relevant articles and generate inclusion criteria.

### Literature search

A systematic electronic search of relevant articles published from January 1999 through to January 2020 was performed using databases, including PubMed, Embase, Scopus, and Cochrane. The search strategy involved the use of a combination of Medical Subject Headings and keywords as follows: "diverticular disease", "DD", "symptomatic uncomplicated diverticular disease", "SUDD", "diverticulitis", "acute diverticulitis", "acute uncomplicated diverticulitis", "mesalazine", "mesalamine", "5-aminosalicylic acid", "5-ASA", "treatment", "therapy". Additional studies were selected after a manual review of the reference lists of the identified studies and review articles.

### Type of studies, population, interventions, comparison, and outcomes

Only articles published in English were selected. Randomised controlled trials (RCTs), open trials, and retrospective studies were included. In these studies, the participants were all patients diagnosed with SUDD or with a history of diverticulitis. We only included studies that analysed primary or secondary outcomes of diverticulitis in patients with a previous diagnosis of SUDD, or recurrence in patients with a history of diverticulitis. All studies compared clinical responses to 5-ASA (irrespective of the dosage regimen) *vs.* placebo, rifaximin, or other treatments. Studies published only as abstracts were excluded. Any discrepancy was resolved by consensus after, referring to the original article.

## Results

### Selection of studies

In Figure 2, the PRISMA diagram summarizes the sequence of the literature selection. Four authors (G. S., A. V., M. V., and F. V.) independently searched through relevant literature and identified 254 articles. Removal of duplicate studies (n = 47) resulted in 207 articles remaining. Among these, 185 articles were excluded after reviewing their titles and abstracts by two authors (G.S., A.V.). The full texts of the remaining 22 articles were then assessed by four authors independently (G.S., A.V., M.V., and F.V.). Among these 22 articles, 10 were excluded because only SUDD cases were analysed (in absence of reported diverticulitis cases). Hence, 12 eligible studies were identified, and these were included in the review. Each of these 12 included articles have been analysed by at least two authors. Any discrepancy was resolved by consensus, referring to the original article.

We separately analysed the studies that evaluated the effectiveness of 5-ASA for the prevention of the first episode of diverticulitis and those that analysed the effectiveness of 5-ASA in preventing the recurrence of diverticulitis.

### 5-ASA for preventing the occurrence of diverticulitis in SUDD

The results of two studies that assessed the efficacy of 5-ASA in the prevention of the first episode of diverticulitis in patients with SUDD are summarized in Table I.

In an open trial, Gatta et al[38] compared the recurrence of diverticulitis in a population of 149 SUDD patients during a five-year follow-up period. In this study, 67 patients were on 5-ASA therapy (1,600 mg/day for 10 days/month), whereas 82 were not on any therapy. Cyclic treatment with 5-ASA was ineffective in reducing the incidence of diverticulitis ($p$=0.1256).

Conversely, in an RCT that included 210 SUDD patients, 5-ASA therapy (1,600 mg/day for 10 days/month) with or without a probiotic (active *Lactobacillus casei subsp.* DG 24 billion/day) was compared with placebo therapy (for 10 days/month) with or without a probiotic. The results demonstrated that acute diverticulitis occurred more frequently in placebo groups than in 5-ASA therapy groups ($p$=0.003)[39].

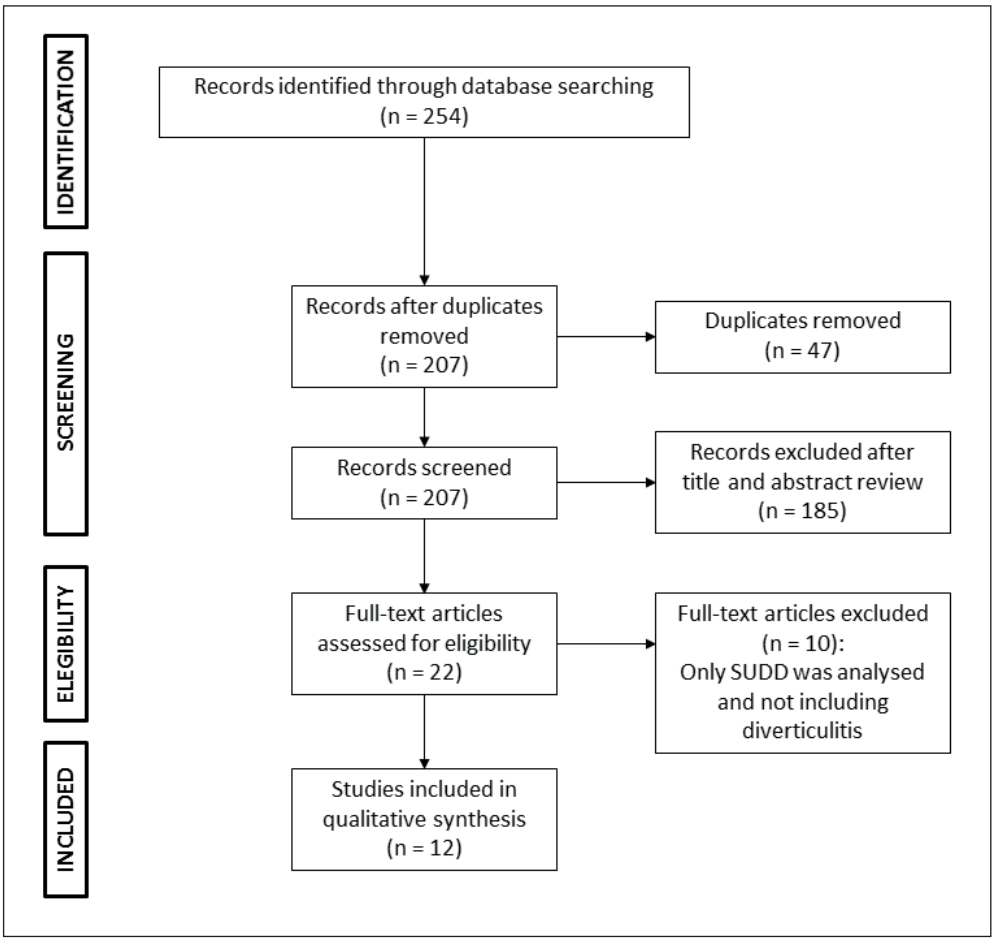


**Figure 2.** The PRISMA diagram shows the sequence of the literature selection and it reports the reasons for the exclusion of some articles.

### *5-ASA in preventing the recurrence of diverticulitis*

The results of ten studies that evaluated the efficacy of 5-ASA in the prevention of the recurrence of diverticulitis are summarized in Table II.

In an open trial, Trepsi et al[40] showed that 5-ASA treatment (800 mg/day for 8 weeks) was more effective than no treatment in reducing the frequency of symptomatic diverticulitis relapse ($p$=0.00005).

Moreover, in an open trial, Tursi et al[41] compared treatment with balsalazide (2,250 mg/day for 10 days/month) plus a probiotic (VSL#3 450 billions/day for 15 days/month) *vs.* treatment with a probiotic alone (VSL#3 450 billions/day for 15 days/month). Their results showed that treatment with balsalazide, which is a 5-ASA formulation, tended to be better than treatment with a probiotic alone in preventing the recurrence of diverticulitis. However, this difference between the two groups was not statistically significant ($p$=0.1).

Conversely, in another open trial, Tursi et al[42] reported that 5-ASA (1,600 mg/day for 7 days/month), in a formulation different to the previously mentioned trial, was more effective than rifaximin (800 mg/day for 7 days/month) in preventing the recurrence of diverticulitis ($p$=0.002).

In yet another open trial[43], the same authors showed that treatment with rifaximin (800 mg/day for 14 days/month) plus 5-ASA (2,400 mg/day for 7 days, followed with 1,600 mg/day for 7 days/month) was more effective than treatment with rifaximin alone (800 mg/day for 14 days/month) in preventing the recurrence of diverticulitis ($p$=0.005).

Nevertheless, in a retrospective study, long-term treatment with rifaximin (800 mg/day for 10 days/month) appeared to be more effective than treatment with 5-ASA (2,400 mg/day for 10 days/month) in preventing the recurrence of diverticulitis ($p$=0.015)[44].

A retrospective study by Tursi et al[45] compared treatment with 5-ASA (1,600 mg/day) for 10 days/month *vs.* treatment with 5-ASA (1,600 mg/day) every day. The long-term outcomes of daily 5-ASA treatment were significantly better than those of intermittent 5-ASA treatment in preventing the occurrence of DD complications ($p$=0.03), including recurrence of diverticulitis.

**Table I.** Mesalazine (5-ASA) in the diverticulitis occurrence in patients with symptomatic uncomplicated diverticular disease (SUDD

| Authors (year) [study design] | Mean follow-up (months) | Number of patients | Disease features | Diagnostic method | Interventions | Diverticulitis occurrence % | Comments |
|---|---|---|---|---|---|---|---|
| Gatta et al[38] (2012) [Open Trial] | 60 | 149:<br>Group M: 67<br>Group C: 82 | SUDD | Positive double-contrast barium enema or colonoscopy | Group M:<br>5-ASA 1600 mg/day (for 10 days/month)<br>Group C:<br>no treatment | Group M:<br>4 %<br>Group C:<br>10.4% | The difference between the two groups was not significant ($p$=0.1256) |
| Tursi et al[39] (2013) [RCT] | 12 | 210:<br>Group M: 51<br>Group L: 55<br>Group LM: 54<br>Group P: 50 | SUDD | Presence of symptoms related to diverticula, in the absence of any complication (stenosis, abscesses, fistulas) | Group M:<br>5-ASA 1600 mg /day + probiotic placebo<br>Group L:<br>5-ASA placebo + active probiotic<br>Group LM:<br>5-ASA 1600 mg /day + active probiotic<br>Group P:<br>5-ASA placebo + placebo probiotic<br>(all patients received treatment for 10 days/month) | Group M:<br>0%<br>Group L:<br>0.5%<br>Group LM:<br>0%<br>Group P:<br>2.9% | Acute diverticulitis occurred significantly more frequently in the placebo groups than in the active 5-ASA treatment groups ($p$=0.003) |

**Table II.** Mesalazine (5-ASA) in the diverticulitis recurrence in patients with previous acute diverticulitis.

| Authors (year) [study design] | Mean follow-up (months) | Number of patients | Disease features | Diagnostic method | Interventions | Diverticulitis occurrence % | Comments |
|---|---|---|---|---|---|---|---|
| Trepsi et al[40] [Open Trial] | 48 | 166<br>Group M: 81<br>Group C: 85 | Previous acute diverticulitis | Positive colonoscopy, or radiological findings, and symptoms, and laboratory findings | Group M:<br>5-ASA 800 mg/day (for 8 weeks)<br>Group C:<br>no treatment | Group M: 7.2%<br>Group C: 23.5% | Treatment with 5-ASA proved to be effective in reducing the frequency of symptomatic relapses ($p$=0.00005) |
| Tursi et al[41] [Open Trial] | 12 | 30<br>Group A: 15<br>Group B: 15 | Previous acute uncomplicated diverticulitis | Positive colonoscopy, and symptoms, and laboratory findings | Group A:<br>Balsalazide 2250 mg/day (for 10 days/month) + probiotic (for 15 days/month)<br>Group B:<br>Probiotic (for 15 days/month) | Group A: 13%<br>Group B: 20% | The difference was not statistically significant between the two groups ($p$<0.1) |
| Tursi et al[42] [Open Trial] | 24 | 111:<br>Group A: 59<br>Group B: 52 | Previous acute uncomplicated diverticulitis | Positive CT and colonoscopy | Group A:<br>5-ASA 1600 mg/day<br>Group B:<br>Rifaximin 800 mg/day (for 7 days/month) | Clinical remission:<br>Group A: 94%<br>Group B: 74% | Patients taking 5-ASA had a lower risk of diverticulitis recurrence than patients taking rifaximin ($p$=0.002) |
| Tursi et al[43] (2002) [Open Trial] | 12 | 218:<br>Group A: 109<br>Group B: 109 | Previous acute diverticulitis | Positive colonoscopy or double contrast X-ray, and symptoms, and laboratory findings | Group A:<br>Rifaximin 800mg /day + 5-ASA 2400mg/day (for 7 days/month), followed by Rifaximin 800mg/day + 5-ASA 1600mg/day (for 7 days/month)<br>Group B:<br>Rifaximin 800mg/day (for 14 days/month) | Group A: 1.4%<br>Group B: 5.9% | Rifaximin plus 5-ASA was more effective than rifaximin alone in the prevention of diverticulitis recurrence ($p$=0.005) |

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**Table II (Continued).** Mesalazine (5-ASA) in the diverticulitis recurrence in patients with previous acute diverticulitis.

| Authors (year) [study design] | Mean follow-up (months) | Number of patients | Disease features | Diagnostic method | Interventions | Diverticulitis occurrence % | Comments |
|---|---|---|---|---|---|---|---|
| Festa et al[44] (2017) [Retrospective] | 15 | 124:<br>Group R: 72<br>Group M: 52 | Previous acute diverticulitis | Positive CT and symptoms, and laboratory findings | Group R:<br>Rifaximin 800mg/day (for 10 days/month)<br>Group M:<br>5-ASA 2400 mg/day (for 10 days/month) | Group R: 9.7%<br>Group M: 26.9% | Long-term treatment with rifaximin was more effective than 5-ASA in preventing diverticulitis recurrence ($p$=0.015) |
| Tursi et al[45] (2013) [Retrospective] | 36 | 311:<br>Group A:207<br>Group B: 104 | Previous acute uncomplicated diverticulitis | Positive CT and laboratory findings | Group A:<br>5-ASA 1600 mg/day (for 10 days/month)<br>Group B:<br>5-ASA 1600mg/day (every day) | Group A: 8.2%<br>Group B: 2.9% | Long-term daily 5-ASA therapy was significantly better than intermittent 5-ASA therapy in preventing DD complications (diverticulitis, bleeding and need of surgery) ($p$=0.03) |
| Kruis et al[46] (2017) [RCT] | 12-24 | 657:<br>Group A: 165<br>Group B: 168 (48 weeks)<br>Group C: 90<br>Group D: 123<br>Group E: 111 (96 weeks) | Previous left-sided acute uncomplicated diverticulitis | Positive US or CT, and symptoms and laboratory findings | Group A: 5-ASA 3000mg/day<br>Group B: placebo (48 weeks)<br>Group C: 5-ASA 3000mg/day<br>Group D: 5-ASA 1500mg/day<br>Group E: placebo (96 weeks) | Group A: 18.8%<br>Group B: 11.9%<br>Group C: 27.6%<br>Group D: 33.3%<br>Group E: 38.5% | 5-ASA was not superior to placebo in preventing diverticulitis recurrence ($p$=0.226 for group A *vs.* B) ($p$=0.980 for group C vs.E) |

*Continued*

**Table II (Continued).** Mesalazine (5-ASA) in the diverticulitis recurrence in patients with previous acute diverticulitis.

| Authors (year) [study design] | Mean follow-up (months) | Number of patients | Disease features | Diagnostic method | Interventions | Diverticulitis occurrence % | Comments |
|---|---|---|---|---|---|---|---|
| Parente et al[47] (2013) [RCT] | 24 | 92:<br>Group M: 45<br>Group P: 47 | Previous acute uncomplicated diverticulitis | Positive US or CT, and symptoms, and laboratory findings | Group M:<br>5-ASA 1600mg/day (for 10 days/month)<br>Group P:<br>Placebo | Group M: 11%<br><br><br>Group P: 28% | Intermittent prophylaxis with 5-ASA did not significantly reduce the risk of diverticulitis relapse ($p$=0.17) |
| Stollman et al[48] (2013) [RCT] | 12 | 117:<br>Group A: 40<br>Group B. 36<br>Group C: 41 | Previous acute diverticulitis | Positive CT | Group A:<br>5-ASA 2400mg/day<br>Group B:<br>5-ASA 2400mg /day + probiotic<br>Group C:<br>placebo (for 10-14 days/months for 12 weeks) | Group A: 28%<br><br>Group B: 37%<br><br>Group C: 31% | Diverticulitis recurrence was comparable across groups |
| Raskin et al[49] (2014) [RCT] | 24 | 583 (prevent 1):<br>Group A: 147<br>Group B: 143<br>Group C: 143<br>Group D: 150<br>586 (prevent 2):<br>Group A: 142<br>Group B: 148<br>Group C: 147<br>Group D: 149 | Previous acute diverticulitis | Positive CT, or MRI, or US, or barium enema, and colonoscopy or sigmoidoscopy, and laboratory findings | Group A:<br>Placebo<br>Group B:<br>5-ASA 1200mg/day<br>Group C:<br>5-ASA 2400mg /day<br>Group D:<br>5-ASA 4800mg/day<br>(both in prevent 1 and 2)<br>(for 104 weeks) | Diverticulitis recurrence-free rate:<br>(prevent 1):<br>Group A<br>64.6%<br>Group B – C – D<br>62.2 – 62.9 – 52.7%<br>(prevent 2):<br>Group A<br>67.6%<br>Group B – C – D<br>62.8 – 59.2 – 69.1% | 5-ASA did not reduce the rate of diverticulitis recurrence<br>(prevent 1):<br>($p$=0.780 for group B *vs.*A)<br>($p$=0.741 for group C *vs.* A)<br>($p$=0.047 for group D *vs.* A)<br>(prevent 2):<br>($p$=0.368 for group B *vs.* A)<br>($p$=0.159 for group C *vs.* A)<br>($p$=0.778 for group D *vs.* A) |

Conversely, four RCTs showed that 5-ASA did not prevent the recurrence of diverticulitis[46-49].

Kruis et al[46] compared 5-ASA therapy (3,000 or 1,500 mg/day) *vs.* placebo therapy. They reported that 5-ASA was not superior to placebo in preventing the recurrence of diverticulitis ($p$=0.226).

Parente et al[47] also compared 5-ASA therapy (1,600 mg/day for 10 days/month) and placebo therapy. They found that intermittent prophylaxis with 5-ASA did not reduce the risk of diverticulitis relapse ($p$=0.17).

Furthermore, Stollman et al[48] compared 5-ASA therapy (2,400 mg/day), with or without probiotics, *vs.* placebo therapy. In this article, the authors showed that the recurrence of diverticulitis was comparable among the two groups. Treatment with probiotics combined with mesalamine did not have increased efficacy.

Finally, Raskin et al[49] compared 5-ASA (1,200 mg or 2,400 mg or 4,800 mg/day) *vs.* placebo therapies and reported that 5-ASA did not reduce the recurrence rate of diverticulitis.

## Discussion

The treatment regimens for the various forms of DD (diverticulosis, SUDD, SCAD, and diverticulitis) are different. In clinical practice, outside of strong scientific evidence, patients with diverticulosis commonly undergo therapy, including specialised dietary regimens, treatment with probiotics, rifaximin, and 5-ASA[32]. According to the results of the most recent meta-analyses, the efficacy of 5-ASA in the prevention of diverticulitis is uncertain[33-37,50-52].

The hypothesis that 5-ASA could be effective for preventing DD comes from two observations: the topical anti-inflammatory mechanism of action of the drug, and its efficacy in treating mild-to-moderate inflammation in cases of UC. Hence, considering that 5-ASA is the first line of treatment for preventing relapse in UC[53], it is conceivable that 5-ASA can be effective in preventing the occurrence or relapse of diverticulitis as well.

The rationale of 5-ASA therapy in preventing the recurrence of diverticulitis could be because of the presence of mild chronic inflammation in DD, which may be the cause of diverticulitis and its recurrence[35]. Obesity, unhealthy diet, and physical inactivity have been identified as risk factors for DD because they influence inflammation and the intestinal microbiome as well[1,54].

Recent literature has shown that only 1-4% of patients with DD will develop diverticulitis[15]. Notably, recurrence of diverticulitis is a frequent and significant clinical event[33,35], occurring in approximately 20% of patients with a history of diverticulitis[1,35].

In the present review, two studies[38,39] analysed the efficacy of 5-ASA in the prevention of the first episode of diverticulitis in patients with SUDD; only one demonstrated the superiority of 5-ASA over placebo[39].

Two systematic reviews[51,52] analysed the role of 5-ASA in the prevention of the first episode of diverticulitis in patients with SUDD.

Based on the results of one of the systematic reviews[51] and of the meta-analysis[37], 5-ASA appeared to be effective for the primary prevention of diverticulitis in patients with SUDD.

The first systematic review included six trials that enrolled 1,021 patients (526 patients were treated with 5-ASA and 495 with placebo or other therapies). Four studies provided information on the occurrence of diverticulitis during the follow-up period, with only one being an RCT. Overall, diverticulitis occurred in 4 out of 382 patients (1.1%) who underwent 5-ASA treatment, and in 6 out of 50 patients (12.0%) who underwent placebo treatment[51].

However, the results of the second systematic review showed that regarding the likelihood to develop acute diverticulitis, there was no difference between SUDD patients on 5-ASA and controls (three trials, 484 participants, Relative Risk [RR] = 0.26, 95% Confidence Interval [CI] = 0.06–1.20)[52]. The authors concluded that for patients with SUDD, 5-ASA can reduce the number of the SUDD recurrences (symptoms relief) without, however, preventing the development of acute diverticulitis.

Two recent meta-analysis[34,37] investigated the role of 5-ASA in the prevention of diverticulitis in SUDD patients.

The first one investigated the effect of 5-ASA on the recurrence of diverticulitis in SUDD patients through a meta-analysis with trial sequential analysis of six RCTs that enrolled a total of 1,918 patients (1,292 in the 5-ASA group, and 626 in the placebo group). Overall, they found no difference between the recurrence of diverticulitis in the 5-ASA group and that of the placebo group (OR=1.20, 95% CI=0.96-1.50, $p$=0.11). Surprisingly, when the 5-ASA dose was > 2 g/day, the risk of diverticulitis recurrence was higher in the 5-ASA group than in the control group (OR=1.28, 95% CI=1.02-1.62, $p$=0.04)[34].

In the second meta-analysis including the data of four RCTs that enrolled 379 patients with SUDD (197 treated with 5-ASA, and 182 with placebo), 5-ASA was effective in preventing the occurrence of diverticulitis in SUDD patients[37]. However, out of these four RCTs, which compared the efficacy of 5-ASA irrespective of the dosage, only two studies provided information regarding the occurrence of diverticulitis during follow-up. Diverticulitis occurred in 19.3% of patients in the 5-ASA group and 33.3% of patients in the placebo group (Odds Ratio [OR]=0.35, 95% CI=0.17-0.70, $p$=0.003 in favour of the 5-ASA group)[39,55]. However, the data from one of these two trials have only been published in an abstract[55]. The other two trials included in the meta-analysis only provided data on the relief of symptoms. It was achieved in 80% of patients in the 5-ASA group, and in 62.7% of patients in the placebo group (OR=0.43, 95% CI=0.24-0.75, $p$=0.003 in favour of the 5-ASA group)[56,57]. Overall, out of the trials that assessed the effectiveness of 5-ASA in preventing the occurrence of diverticulitis, two[39,55] presented favourable results and one[38] showed unfavourable results.

Regarding the evaluation of the efficacy of 5-ASA in preventing the recurrence of diverticulitis, ten studies (four open studies, two retrospective series, and four RCTs) were analysed in the present review.

The results of three open[40,42,43] and one retrospective[45] studies showed that 5-ASA had a certain degree of efficacy.

Whereas, all four RCTs demonstrated that 5-ASA did not significantly reduce the rate of diverticulitis recurrence[46-49].

In a retrospective trial, 5-ASA was found to be less effective than rifaximine in preventing the recurrence of diverticulitis[44].

In an open trial, there was no difference between the efficacy of 5-ASA treatment and probiotic treatment in preventing the recurrence of diverticulitis[41].

The overall results that emerged from the analysis of these last ten studies are in line with the results of several meta-analyses that showed that the role of 5-ASA in the prevention of diverticulitis recurrence is still uncertain[33,36,50,58].

Khan et al[36], in their meta-analysis, assessed the efficacy of 5-ASA in preventing the recurrence of acute diverticulitis. They included four RCTs, which enrolled 1,423 patients with a history of diverticulitis (one of the four RCTs was made up of two parallel RCTs, making a total of five RCTs). They reported that 5-ASA did not help prevent the recurrence of acute colonic diverticulitis (RR=0.99, 95% CI= 0.74-1.34, $p$ = 0.13).

A meta-analysis by Carter et al[33] included seven studies with a total of 1,805 participants with a history of diverticulitis. Authors found that 5-ASA therapy was not more effective than placebo therapy in preventing the recurrence of diverticulitis (31.3% *vs.* 29.8%; RR=0.69, 95% CI=0.43-1.09). However, considering the unclear role of 5-ASA in the prevention of diverticulitis and the low quality of existing evidence, the authors recommended no modifications in actual therapeutic strategies. Overall, the quality of the evidence on the efficacy of 5-ASA in preventing the recurrence of diverticulitis was very low owing to study limitations and the significant heterogeneity in the meta-analysis[33,35]. This meta-analysis included three open trials[40,41,43] and four RCTs[47-49].

A recent meta-analysis included seven articles (two abstracts and five full published articles), with a total of eight RCTs (one of the studies was made up of two parallel RCTs, making a total of eight RCTs) and enrolled 2,314 patients with a history of diverticulitis. It reported that 5-ASA was not superior to placebo in preventing the recurrence of diverticulitis (RR=0.86, 95% CI=0.63-1.17)[50]. Five trials compared 5-ASA therapy with placebo therapy[47,49,56,59]. In one study, balsalazide (as 5-ASA) was administered to patients in the intervention group, and probiotics were administered to patients both in the intervention and control groups[41]. 5-ASA, placebo, and 5-ASA plus probiotics treatments were compared in one study[48], whereas another study[43] compared treatment with a combination of 5-ASA and rifaximin with treatment with rifaximin alone.

In the recent National Institute for Health and Care Excellence (NICE) guidelines on DD, the comparison of different doses of 5-ASA, the comparison of 5-ASA and placebo, and the comparison of 5-ASA plus probiotic and probiotic alone confirmed that 5-ASA is not effective in preventing acute diverticulitis[58].

An observation can be made based on the findings of the RCTs included in the present review. The only study that involved the use of high doses of 5-ASA (> 4,000 mg/day) showed a trend toward greater efficacy in the group treated with 4,800 mg/day compared with the placebo group (prevent 1: $p$=0.047)[49]. Notably, the formulation that was used in this study releases 5-ASA mostly in the distal colon, the site where diverticula more frequently occur. However, the NICE review

judged the evidence from this study to have a very high risk of bias due to its low quality[58].

However, it has been demonstrated that 5-ASA has a dose-dependent effect in cases of UC. UC patients that are at high risk of relapse, e.g., patients with extensive UC or with frequent relapses– benefit from high doses of 5-ASA as maintenance therapy[60,61].

Therefore, it could be argued that the prevention of diverticulitis could result from a dose-dependent effect of 5-ASA, and patients with a high risk of a flare-up should be treated with high doses of 5-ASA.

Also, it is important to consider that 5-ASA is generally well tolerated, though various side effects could occur, such as nephropathies, hepatotoxicity, pancreatitis, cardiotoxicity, inflammatory reactions, musculoskeletal complaints, respiratory symptoms, and sexual dysfunction.

To note that a recent systematic review concluded that the occurrence of these side effects did not depend on 5-ASA dose[62].

## Conclusions

To date, evidence on the efficacy of 5-ASA therapy in the prevention of diverticulitis are conflicting, both for SUDD patients and those with a history of diverticulitis. Effective medical strategies for the prevention of diverticulitis are needed. Further rigorous and well-designed randomised, double-blinded, placebo-controlled trials that include groups of patients with more homogeneous characteristics are also warranted to define the role and usefulness of 5-ASA in the management of DD, especially in the prevention of diverticulitis.

### Authors' Contribution

All authors have read and approved the manuscript.

### Conflict of Interests

The authors declare no conflict of interest.

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