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REVIEW ARTICLE

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# The role of microbiota and its modulation in colonic diverticular disease

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## Abstract

**Background:** Diverticular disease (DD) is a common condition in Western countries. The role of microbiota in the pathogenesis of DD and its related symptoms has been frequently postulated since most complications of this disease are bacteria-driven and most therapies rely on microbiota modulation. Preliminary data showed fecal microbial imbalance in patients with DD, particularly when symptomatic, with an increase of pro-inflammatory and potentially pathogenetic bacteria. In addition, bacterial metabolic markers can mirror specific pathways of the disease and may be even used for monitoring treatment effects. All treatments currently suggested for DD can affect microbiota structure and metabolome compositions.

**Purpose:** Sparse evidence is available linking gut microbiota perturbations, diverticular disease pathophysiology, and symptom development. We aimed to summarize the available knowledge on gut microbiota evaluation in diverticular disease, with a focus on symptomatic uncomplicated DD, and the relative treatment strategies.

**KEYWORDS**
diverticular disease, diverticulosis, fecal microbiota transplantation, fiber, mesalazine, metabolome, microbiota, probiotics, rifaximin, symptomatic uncomplicated diverticular disease

## 1 | INTRODUCTION

Diverticular disease (DD) is an extremely common condition in Western countries,[1,2] with a prevalence of colonic diverticula ranging from 5% before the age of 40, up to 50% around 60 years.[3] The presence of diverticula in asymptomatic subjects is termed diverticulosis, while DD spans a wide spectrum of clinical entities, including symptomatic uncomplicated diverticular disease (SUDD), uncomplicated and complicated diverticulitis, and segmental colitis associated with diverticulosis (SCAD).[1]

SUDD is defined as the concomitant presence of colonic diverticula without overt inflammation seen at colonoscopy or computed tomography with symptoms resembling those of the irritable bowel syndrome (IBS), such as abdominal pain, abdominal bloating, and changes in bowel habits.[1,4–6] It has been estimated that around 20%–25% of patients with colonic diverticula suffer from SUDD and that the lifetime risk of acute diverticulitis is 10%–25%.[7] The causes and timing of a shift from diverticulosis to SUDD are still not clear.[8] There is now increasing evidence supporting a role for gut microbiota in the pathogenesis of digestive and extra-digestive diseases.[9–13]

Giovanni Marasco and Francesco Buttitta contributed equally to this work and shared co-first authorship.

Gut microbiota is able to shape host's innate and adaptive immunity through specific interactions between gut bacteria and mucosal immune cells; this continuous relationship is crucial for immune tolerance and control of inflammation and is at the basis of immunological homeostasis.[14–16] Microbial homeostasis is also characterized by a proper balance between protective resident microorganisms and pathobionts (i.e., any potentially pathological organism which, under normal circumstances, lives as a non-harming symbiont). Once this balance is disrupted, a condition named dysbiosis can occur, which has been linked to several gastrointestinal diseases,[10,11,14,17–20] including diverticular disease.[21] Indeed, the role of microbiota in the pathogenesis of diverticular disease and its related symptoms has been frequently postulated since most complications of this disease are bacteria-driven and most therapies rely on microbiota modulation (Figure 1).[22] Preliminary data showed a microbial imbalance in the fecal microbiota of patients with diverticular disease, particularly when symptomatic, with an increase of pro-inflammatory and potentially pathogenetic bacteria.[21,22] However, scant and sparse evidence is available linking gut microbiota perturbations, diverticular disease pathophysiology, and symptom development.[10,23–25] We aimed to summarize the available knowledge on gut microbiota evaluation in diverticular disease, with a focus on SUDD, and the relative treatment strategies.

**Key points**

- Dysbiosis plays a central role in the etiopathogenesis of diverticula and symptoms development.
- Treatments currently suggested for diverticular disease can affect microbiota structure and metabolome compositions.
- Further studies are needed to clarify the pathophysiological mechanisms by which microbial shifts following different therapeutic strategies can lead to symptom control and acute diverticulitis prevention.

## 2 | METHODS

Identification of studies on gut microbiota assessment and modulation in diverticular disease were carried out with literature search up to September 10, 2022, with MEDLINE via PubMed, Ovid Embase, and Scopus using the following medical subject heading (MESH) terms 'diverticular disease' OR 'diverticula' OR 'diverticulosis' OR 'SUDD' OR 'diverticulitis' AND 'microbiota' OR 'microbial' OR 'microflora' was performed by two authors (GM and FB). Articles more relevant for the topic of this clinical review were selected without language or time restriction; references of selected articles and systematic reviews were also evaluated, when of interest.

## 3 | MICROBIOTA IN DIVERTICULAR DISEASE

Only few studies aimed at profiling gut microbiome in diverticular disease and even fewer tried to assess gut metabolome. No differences were found in microbiota composition and mucosal lymphocyte counts in asymptomatic diverticulosis patients compared to controls; moreover, microbiota diversity in both sigmoid and transverse colon was similar.[26] No differences in microbiota richness or diversity between patients with or without diverticulosis were also found in a large Swedish study, which additionally reported that patients with diverticulosis with a higher abundance of genus *Comamonas* were more likely to later develop acute diverticulitis.[27] On the contrary, a microbial shift with a decrease in Bacteroidetes and an increase in Firmicutes was found in patients with uncomplicated diverticular disease.[28] Firmicutes to Bacteroides rate gradually increased from healthy subjects to patients with diverticular disease, IBS, and inflammatory bowel diseases (IBD) patients.[28] Bacteroidetes and Firmicutes are usually the two dominant phyla in the healthy gut microbiome; a difference in their relative proportion has been associated with the concept of dysbiosis and the occurrence of gastrointestinal diseases.[29] These data were not confirmed in other SUDD cohorts compared to controls.[30,31]

We recently described[21] that patients with diverticulosis and SUDD showed a decrease in *Clostridium cluster IV* and *Clostridium cluster IX*, whereas SUDD patients showed a significant decrease in anti-inflammatory and protective clusters such as *Fusobacterium* and *Lactobacillaceae* compared to asymptomatic diverticulosis. *Clostridium cluster IV* is a bacterial group encompassing several anti-inflammatory and butyrate-producing species, such as *Faecalibacterium prausnitzii*, whereas *Clostridium cluster IX* produce propionate, which has health-promoting effects, including anti-lipogenic, cholesterol-lowering, anti-inflammatory, and anti-carcinogenic action.[32] However, a recent report failed in finding *Faecalibacterium prausnitzii* differences between healthy, diverticulosis, and SUDD patients.[33]

Importantly, we[21] found that the abundance of both *Akkermansia* and members of the *Clostridium cluster IV* were inversely correlated with macrophages in the peri-diverticular region, confirming that their depletion may have a pro-inflammatory effect thus leading to symptom development. Similar data[34] on macrophages have been reported in a subsequent study which additionally showed that nerve fiber sprouting was increased only in the diverticular region of patients with SUDD, thus suggesting a role in symptom generation. In contrast, Tursi et al.[30] found a significant increase in fecal *Akkermansia muciniphila* in SUDD compared to diverticulosis and controls. However, *Akkermansia muciniphila* is a symbiont inhabiting our gastrointestinal tract and accounting up to 4% of the total colonic microbiota.[35] Its decrease has been associated with several diseases such as IBD,[36] celiac disease,[10,37] appendicitis,[38] and metabolic syndrome and obesity.[39] The members of the *Akkermansia* family are considered a biomarker of a healthy gut.[38,40] These bacteria can colonize the mucus leading to its degradation to production of

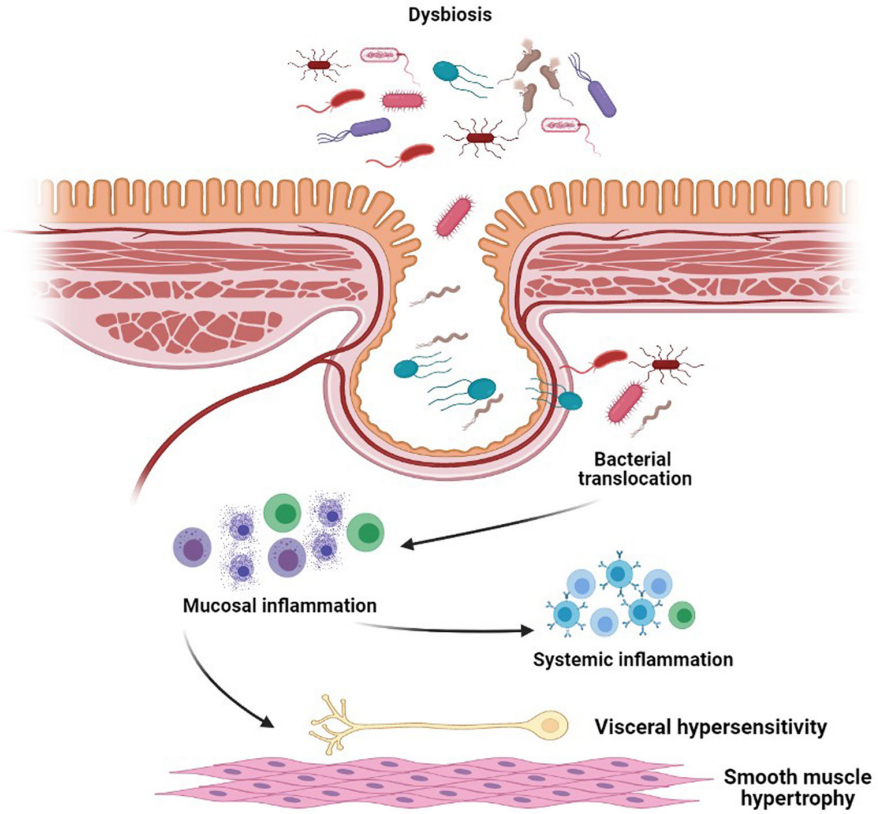


**FIGURE 1** Pathophysiology of clinical manifestations in symptomatic uncomplicated diverticular disease.

acetate and propionate.[41] They can also have a homeostatic role in the microbial composition following pathogenic infections, through the production of oligosaccharides and short-chain fatty acids. Interestingly, *Akkermansia muciniphila* species have been reported to be reduced at the end and after 30 days subsequent to different treatments modulating microbiota in SUDD patients in a recent report.[42]

Gut microbial signatures have also been linked to symptom patterns in patients with SUDD. A cross-sectional study showed that the severity of abdominal bloating was significantly related to higher abundances of *Ruminococcus* and lower abundance of *Roseburia*.[43] This may be explained by the fact that *Ruminococcus* is a hydrogen-producing bacteria through a carbohydrate fermentation process in the gut, while *Roseburia* is capable of producing butyrate, a SCFA that promotes gut motility and reduces hypersensitivity[32,43] (Table 1). In acute diverticulitis, an increased diversity in *Proteobacteria*, in particular *Enterobacteriaceae*, was found in patients with a first episode of uncomplicated acute diverticulitis than in healthy controls.[31] *Proteobacteria* are a less abundant phyla present in the gastrointestinal tract and an increase in their relative abundance is considered an important marker of dysbiosis, being associated with several pro-inflammatory conditions including IBD.[44] Within *Proteobacteria*, the *Enterobacteriaceae* family group is a Gram-negative cluster that can promote and amplify mucosal inflammation due to the enormous quantity of bacterial antigens and micro metabolites.[45] This makes plausible an increase in the abundance of this cluster during inflammation. However, no data exist explaining whether this imbalance cause diverticula inflammation or it is an epiphenomenon of this process. A recent meta-analysis including patients with diverticular disease found that an increase in *Enterobacteriaceae* seems to be the signature more frequently associated with the disease, although acute diverticulitis was evaluated in only one of the included studies.[46] Additionally, a recent study[47] comparing gut microbiota of patients with ongoing acute diverticulitis compared to controls, which were defined as patients without a previous history of acute diverticulitis, found that patients with acute diverticulitis had a lower abundance of commensal bacterial families such as *Lachnospiraceae*, *Ruminococcus*, and *Faecalibacterium* than controls, and there was an increase in several genera with known pathogenic roles including *Fusobacteria*, *Prevotella*, and *Paraprevotella*.[47] Therefore, this study further supports the hypothesis that alterations in the colonic microbiome play a role in the pathogenesis of acute diverticulitis.[47] In conclusion, up to now no data are available regarding a possible effect of microbial imbalances on diverticula development. Microbial imbalances seem to be linked to symptom presence, and some microbial signatures seem to be linked to symptom patterns in patients with diverticular disease.

## 4 | METABOLOME IN DIVERTICULAR DISEASE

The search for non-invasive and easy-to assess biochemical and clinical markers in diverticular disease has been recently focused on metabolomic aspects. Metabolome is the comprehensive collection of all the metabolites present in a tissue, cell or specimen,

**TABLE 1** Assessment of gut microbiota in diverticular disease.

| Author | Year | Patients (*n*) and disease | Samples | Analytic technique | Outcome |
|---|---|---|---|---|---|
| Daniels et al.[31] | 2014 | • 31 uncomplicated acute diverticulitis<br>• 25 healthy controls | Fecal | PCR-based profiling | Higher diversity in *Proteobacteria* in patients than in controls ($p<0.0002$).<br>No differences in the *Bacteroidetes/Firmicutes* ratio. |
| Tursi et al.[30] | 2016 | • 15 SUDD<br>• 13 asymptomatic diverticulosis<br>• 16 healthy controls | Fecal | RT-PCR on targeted microorganisms | No significant differences in microbiome abundance across groups.<br>*Akkermansia* more represented in patients than controls ($p=0.017$). |
| Kvasnosvky et al.[43] | 2017 | • 28 SUDD | Fecal | Metagenomics (16S RNA microbial profiling) | High *Ruminococcus* and low *Roseburia* correlated to higher bloating severity index score ($p=0.032$ and $p=0.002$). |
| Barbara et al.[21] | 2017 | • 8 SUDD<br>• 16 diverticulosis<br>• 14 healthy controls | Fecal | Metagenomics (16S rRNA microbial profiling) | *Clostriudium IX* depletion in SUDD and diverticulosis ($p=0.03$) vs. controls.<br>*Fusobacterium* and *Lactobacillaceae* depletion in SUDD vs. diverticulosis ($p=0.05$). |
| Schieffer et al.[134] | 2017 | • 9 diverticular disease | Mucosa biopsies during surgery | 16S rRNA + fungal ITS sequencing | *Microbacteriaceae* and *Basidiomycota* increased in diverticular regional vs. adjacent tissue |
| Lopetuso et al.[28] | 2018 | • 4 diverticular disease<br>• 8 healthy controls | Fecal | Metagenomics (16S RNA microbial profiling) | Similar fecal microbiota composition between patients and controls, except for a *Bacteroides fragilis* depletion in patients. |
| Laghi et al.[42] | 2018 | • 13 SUDD | Fecal | RT-PCR on targeted microorganisms | Little differences in microbiome composition across groups. |
| Jones et al.[135] | 2018 | • 226 diverticulosis<br>• 309 healthy controls. | Mucosa biopsies during colonoscopy | Metagenomics (16S RNA microbial profiling) | Differences for phylum *Proteobacteria* ($p=0.038$) and family *Comamonadaceae* ($p=0.035$) across groups. |
| van Rossen et al.[26] | 2021 | • 24 diverticular disease<br>• 19 controls | Mucosa biopsies during colonoscopy | PCR 16S-23S IS profiling | Microbiota diversity in both sigmoid and transverse colon was similar between groups. |
| O'Grady et al.[47] | 2022 | • 65 acute diverticulitis<br>• 27 controls | Rectal swab samples | 16S rRNA sequencing | Decrease of *Lachnospiraceae, Ruminococcus, and Faecalibacterium* and increase in *Fusobacteria, Prevotella, and Paraprevotella* in acute diverticulitis vs. controls. |

Abbreviations: *n*, number; PCR, polymerase chain reaction; RT, real-time; SUDD, symptomatic uncomplicated diverticular disease.

involved in specific signaling pathways.[48] The assumption is that specific metabolic pathways may be involved in symptom generation, so that metabolome evaluation has been postulated to be a more accurate target in defining this relationship. Patients with DD are characterized by different metabolic patterns in symptomatic and asymptomatic scenarios.[30] A study by Tursi et al.[30] described significant differences in several fecal metabolites (N-acetil-compounds and an unclassified metabolite called U1) among healthy controls, asymptomatic diverticulosis, and SUDD. Different metabolic urinary signatures allowed to discriminate among the cohorts: urinary hippurate was significantly higher in asymptomatic diverticulosis compared to healthy controls, whereas methanol levels were significantly higher in asymptomatic diverticulosis compared to SUDD patients and healthy controls.[49]

On the same line, we showed[21] that urinary hippurate level was significantly lower in SUDD patients than in diverticulosis or controls and that urinary X-5.43, a conjugate saccharide, was higher in diverticulosis compared to controls. We also showed that kynurenine, a catabolite of tryptophan metabolism, was present in higher levels in SUDD patients compared to controls.[21] These metabolic perturbations support a biological plausibility for symptom presence in patients with diverticula. As an example, hippurate, which is the glycine conjugate of benzoic acid, results from the metabolic conversion by gut microbes of dietary aromatic compounds to benzoate.[50] Perturbations in hippurate urinary levels are often attributed to changes in gut microbial activities and compositions, such as changes in the abundance of *Bacteroidaceae*.[51] By a functional point of view, benzoate has potential anti-inflammatory properties[52] and therefore, low levels of hippurate may be associated with a decreased anti-inflammatory potential. Kynurenine, which is part of the catabolic pathway of tryptophan, may impact gut function and the mucosal immune system, hence being of potential relevance for the pathophysiology of diverticular disease, other than being previously associated with the pathogenesis of several gastrointestinal disorders.[53] Therefore, the metabolite profiles of patients with diverticular disease may be linked to inflammation and gut neuromotor dysfunction.[21] A subsequent study showed differences in 18 metabolites up to 30 days after several therapies (fibers, probiotics, mesalazine, rifaximin) administered to SUDD patients,[42] while metabolite profile at 60 days resembled that found before treatment.[42] In conclusion, metabolic markers can mirror specific pathways of the disease and may be even used for monitoring treatment effects.

## 5 | MICROBIOTA MODULATION

### 5.1 | Fiber supplementation

Fiber intake has a great impact on gut bacteria ecology. Indeed, fibers act as a prebiotic in the gut since they are metabolized by the gut microbiome, leading to the production of SCFAs like butyrate, which has anti-inflammatory and protective properties.[54] Indeed, a fiber and carbohydrates-rich based diet can lead to a predominance in *Prevotella* enterotype, whereas a fat and protein-rich westernized diet produces a shift towards *Bacteroides* enterotypes.[55] *Prevotella* genus is associated with a higher production of SCFAs, that enhance colonic mucus and antimicrobial peptide production, enhancing functional intestinal barrier, eubiosis and reducing inflammatory gut environment.[56] In particular, a diet rich in whole grain and barley was associated with an increased *Prevotella/Bacteroides* ratio and consequently to beneficial effects on systemic and gut homeostasis.[57] Given this rationale, modulating the microbiome with a based-fiber diet or with fiber supplementation could impact on diverticular disease occurrence and symptom management, although additional clinical evidences are needed to better support their use in clinical practice (Table 2).

The pathogenesis of diverticular disease has been linked to a low dietary fiber intake leading to a decreased fecal mass and therefore, according to Laplace's law, to an increased pressure against the colonic wall, favoring the formation of diverticula.[58] A recent large systematic review and meta-analysis with over 19,000 cases and over 865,000 participants suggested that a high dietary fiber intake (30 g per day) may have a 41% risk reduction in developing diverticular disease compared to subjects with a lower fiber intake.[59] Besides, "The Million Women Study" included a large cohort of middle-aged women without known diverticulosis and showed that the risk of developing diverticular disease was significantly reduced in individuals reporting a high dietary fiber intake, mainly fiber from cereal, fruit, and vegetables, compared to those with a lower fiber diet.[60] Nonetheless, conflicting results are available in the Literature, with data suggesting a link between high dietary fiber intake and increased risk of diverticular disease, thus suggesting that classical risk factors related to diverticular disease should be reassessed.[61–63]

As to symptoms in diverticular disease, although some studies suggest that dietary or supplemental fibers could be beneficial in diverticular disease, their role in reducing abdominal symptoms or preventing acute diverticulitis is still debated and high-quality evidence is lacking.[64]

Management of uncomplicated diverticular disease has been historically focused on high dietary fiber or fiber supplementation.[65,66] A recent meta-analysis[67] showed that fiber supplementation was able to increase mean stool weight but had no significant effects on gastrointestinal symptoms and stool transit time.[67] As for acute diverticulitis, a prospective cohort study including 50,019 women found that a high dietary fiber intake, especially from fruit and cereals, was able to reduce the risk of acute diverticulitis, whereas no evidence was found for vegetables fiber.[68] Fiber from fruit and vegetables can also significantly reduce the overall risk of hospitalization for diverticular disease.[69] In conclusion, high-quality evidence on fiber supplementation for the management and prevention of diverticular disease is still inconclusive.[70] Nonetheless, most of national and international guidelines suggest the use of fiber supplementation in diverticular disease.[71,72]

### 5.2 | Probiotics

Probiotics, as defined by the World Health Organization, are live microorganisms that, when administered in adequate amounts confer a health benefit on the host.[73] To date, the role of probiotics in the prevention and treatment of diverticular disease is still not well understood. Probiotics are supposed to have a key role in the modulation of gut microbiome mainly by competing against pathogenic bacteria on colonic molecular substrates, therefore preventing pathological gut colonization.[74,75] Moreover, probiotics can also interact with toll-like receptors (TLRs) in order to suppress colonic inflammation by enhancing immune tolerance: in vitro studies demonstrate that *B. infantis* and *B. breve* can induce expression of regulatory T cells and IL-10 release, while *L. rhamnosus GG* and *L. acidophilus* can inhibit the

**TABLE 2** Main systematic reviews and meta-analyses reporting on fiber administration in diverticular disease.

| Author | Year | Study | Patients (*n*) and disease or trials | Outcome |
|---|---|---|---|---|
| Unlu et al.[70] | 2012 | Systematic review | 3 RCT<br>1 case–control study | Lack of evidence, only recommendations based on level 2 or 3 of evidence. |
| Dahl et al.[136] | 2018 | Systematic review | 8 different studies | No evidence for a low-fiber diet during uncomplicated acute diverticulitis. It is recommended to start with a high fiber diet as soon as the acute episode has resolved. |
| Eberhardt et al.[67] | 2019 | Systematic review and meta-analysis | 6 RCT<br>3 uncontrolled pre-test post-test trials | Lack of evidence, still high dietary fiber is recommended in patients with asymptomatic DD or SUDD. Dietary fiber supplementation should be assessed on an individual basis due to lack of evidence. |
| Aune et al.[59] | 2020 | Systematic review and meta-analysis | 5 prospective cohort studies<br>865,829 patients | Fiber 30 g/day brings 41% reduction in the risk of developing diverticular disease |

Abbreviations: DD, diverticular disease; *n*, number; RCT, randomized controlled trial; RT, real-time; SUDD, symptomatic uncomplicated diverticular disease.

expression of Th17 cells and secretion of IL-23, a pro-inflammatory cytokine.[76] Moreover, gut barrier function can be improved by the ability of some strains of probiotics (as *E. coli Nissle 1917*) to upregulate tight junction protein expression.[77–79] These assumptions have led to the introduction of probiotic administration into the management of diverticular disease (Table 3). In this context, the most used probiotics include *Lactobacilli*, *Bifidobacteria*, and yeasts such as *Saccharomyces boulardi*.[80]

As for symptom control in diverticular disease, a randomized controlled trial[81] showed that the administration of *Lactobacillus paracasei B21060* plus high fiber diet led to a better and faster decrease in bloating and abdominal pain, compared to high fiber diet alone in a SUDD cohort of 45 patients.[81] Similar results were achieved in a trial with administration of *Lactobacillus paracasei F19* plus high fiber diet,[82] while no significant differences have been reported after administration of a probiotic mixture (*Lactobacillus rhamnosus* NCIMB 30174, *Lactobacillus plantarum* NCIMB 30173, *Lactobacillus acidophilus* NCIMB 30175, and *Enterococcus faecium* NCIMB 30176) versus placebo[83] in abdominal pain score in SUDD patients. Notably, patients within the probiotic group improved other abdominal symptoms other than abdominal pain, such as constipation, diarrhea, mucorrhea, and back pain, in up to 40% of cases.

Mesalazine and *Lactobacillus casei subsp. DG*, particularly in combination, appear to be better than placebo, when administered for 10 days/month for 12 months for the prevention of symptom recurrence in SUDD.[84] However, when mesalazine was associated with *Bifidobacterium infantis* did not significantly ameliorate abdominal symptoms when compared to Mesalazine alone in post-acute diverticulitis patients.[85]

Probiotics may exert a positive effect also in the management of acute uncomplicated diverticulitis, as suggested by a recent trial demonstrating that the administration of *L. reuteri 4659* combined to conventional antimicrobial therapy led to a significant reduction in pain, inflammation and in-hospital stay.[86] However, a systematic review including 11 studies failed to confirm the therapeutic efficacy of probiotics in SUDD and acute diverticulitis patients due to the heterogeneity of data, cohorts and outcomes.[87] In conclusion, certain probiotic strains are able to reduce abdominal symptoms in patients with diverticular disease, although we are still far from defining a specific probiotic therapy in each diverticular disease clinical scenario, due to the lack of definitive high-quality evidence.

### 5.3 | Rifaximin

Rifaximin is a poorly absorbable oral antibiotic that has been widely used in the treatment of digestive diseases including diverticular disease.[22,88] Its broad spectrum of action targets gram-positive, gram-negative, aerobic and anaerobic bacteria,[89] even though microbial modulation is modest and only transient.[90] Since diverticula are pouches of the colonic wall predisposed to fecal entrapment, bacterial overgrowth and translocation leading to inflammation, the use of antibiotics with intraluminal availability in diverticular disease has been postulated (Figure 1).[91]

Moreover, rifaximin has an eubiotic effect promoting the growth of beneficial anti-inflammatory bacteria such as *Bifidobacteria*, *Lactobacilli*, and *Faecalibacterium prausnitzii*, without impairing the overall gut microbiome and inducing a reduction in hydrogen-producing bacteria such as *Ruminococcus*, that may play a role in bloating symptoms.[19,92–95] According to recent studies, rifaximin is supposed to have also a low-grade anti-inflammatory property thanks to its capacity of binding to the Pregnane X Receptor (PXR), a cytosolic protein that regulates inflammation and detoxification of xenobiotics,[96] as well as modulating the mucosal adaptive immune system.[97] In murine models of IBS, rifaximin improved visceral hyperalgesia by a microbiota-driven reduction in transient receptor potential vanilloid 1 channels expression (TRPV1, a receptor involved in pain perception) in the gut.[98] In addition, rifaximin is able to increase

**TABLE 3** Main studies reporting on probiotic administration in diverticular disease.

| Author | Year | Study | Patients (*n*) and disease | Probiotic | Therapy | Outcome |
|---|---|---|---|---|---|---|
| Annibale et al.[82] | 2011 | Open RT | 50 SUDD<br>• Group A: 16<br>• Group B: 18<br>• Group C: 16 | Genefilus F19© (*Lactobacillus paracasei F19*) | Group A: high fiber diet alone.<br>Group B: high fiber diet +1 probiotic for 14d per month for 6 m.<br>Group C: high fiber diet +2 probiotic for 14d per month for 6 m. | Groups B and C: decrease in bloating ($p < 0.05$) and in prolonged abdominal pain ($p = 0.016$) |
| Lahner, et al.[81] | 2012 | RCT | 45 SUDD<br>• Group A: 24<br>• Group B: 21 | Flortec© (*Lactobacillus paracasei B21060*) | Group A: probiotic + high fiber diet for 6 months.<br>Group B: high fiber diet for 6 months. | Group A faster reduction in abdominal pain ($p = 0.001$) and reduction in bloating symptoms ($p = 0.005$)<br><3–6 months |
| Tursi et al.[84] | 2013 | RCT | 210 SUDD<br>• Group M: 51<br>• Group L: 55<br>• Group LM: 54<br>• Group P: 50 | Enterolactis Plus© (*L. casei subsp. DG*) | Group M: mesalazine + probiotic placebo<br>Group L: mesalazine placebo + probiotic 1 × 10 day/month<br>Group LM: mesalazine + probiotic 1 × 10 day/month<br>Group P: mesalazine placebo + probiotic placebo | LM group has a higher remission rate vs. group M, L and P ($p = 0.015$, 0.011, 0.000). |
| Stollman et al.[85] | 2013 | RCT | 117 after acute diverticulitis<br>• Group A: 41<br>• Group B: 40<br>• Group C: 36 | Align© (*B. infantis* 35,624) | Group A: placebo.<br>Group B: Mesalazine 2.4 g for 10–14 days for 12 weeks.<br>Group C: Mesalazine 2.4 g for 10–14 days for 12 weeks + probiotic. | Probiotics plus Mesalazine did not achieve significant symptom improvement vs. placebo or Mesalazine alone. |
| Kvasnovsky et al.[83] | 2017 | RCT | 120 SUDD<br>• Group A: 56<br>• Group B: 64 | Symprove© (*L. rhamnosus* NCIMB 30174, *L. bacillus plantarum* NCIMB 30173, *L. acidophilus* NCIMB 30175, *E. faecium* NCIMB 30176) | Group A: probiotic for 3 months<br>Group B: placebo for 3 months | Group A improved frequency of 4 symptoms ($p < 0.04$). No differences in abdominal pain score ($p = 0.11$). |
| Petruzziello et al.[86] | 2019 | RCT | 88 acute uncomplicated diverticulitis<br>• Group A: 44<br>• Group B: 44 | *L. reuteri* 4659 | Group A: Ciprofloxacin 500 mg bid + Metronidazole 500 mg tid + Probiotic bid.<br>Group B: Ciprofloxacin 500 mg bid + Metronidazole 500 mg tid + Placebo bid. | Group A reduction in pain and inflammatory markers.<br>Shorter hospitalization ($p < 0.0001$). |

Abbreviations: *n*, number; RCT, randomized controlled trial; SUDD, symptomatic uncomplicated diverticular disease.

the mean fecal weight and, consequently, to reduce intraluminal pressure by lowering fiber degradation in the gut.[99,100] Therefore, rifaximin and fiber might exert a synergic effect in diverticular disease (Table 4).

A controlled study showed that SUDD patients taking rifaximin 400 mg b.i.d plus fiber supplementation in a 10 days per month cycle had better symptom control than patients taking fiber alone.[101] Another recent large retrospective cohort study[102] with 8 years of follow-up described that SUDD patients taking rifaximin 800 mg/day had reduced abdominal symptom severity, compared to patients taking any other on-demand therapies, while the decrease in acute diverticulitis recurrence did not reach statistical significance.[102] Data on symptom control were confirmed by open randomized trials using rifaximin plus fiber in a 7 days per month cycles, achieving better symptom control as well as better preventing effect on acute diverticulitis recurrence.[103,104] Finally, a meta-analysis found a statistically significant symptom relief [number needed to treat (NNT) 3] and prevention of diverticular complication (NNT 59) in a cohort of patients with SUDD taking rifaximin plus fiber supplementation compared to patients taking fiber alone.[105] However, it is important to recognize that this meta-analysis was based on 4 studies, published between 1992 and 2007, and with an open label design in 3 out of 4 studies included.

Concerning the possible reduction of the risk of progression to acute diverticulitis, in a systematic review the administration of rifaximin and fiber was less likely associated with acute diverticulitis when compared to fiber alone.[106] Besides, a 10-day/month cyclic administration of rifaximin was also safe and effective for the secondary prevention of acute diverticulitis compared to mesalazine.[107]

To our knowledge, only one study[92] prospectively evaluated the effect of rifaximin at the dose of 1200 mg/daily for 10 days in patients with diverticular disease, finding that the microbial alpha diversity was slightly increased in clinical responders and decreased in non-responders, leading to a significant post-treatment increase in *Faecalibacterium* abundance and a decrease in *Ruminococcus* abundance in responders. These data were not confirmed with a rifaximin 800 mg/die for 7 days.[108] Thus, although several studies have been

**TABLE 4** Main studies reporting on Rifaximin administration in diverticular disease.

| Author | Year | Study | Patients (*n*) and disease and/or included studies | Therapy | Outcome |
|---|---|---|---|---|---|
| Papi et al.[137] | 1992 | Open RT | 217 SUDD<br>• Group A: 107<br>• Group B: 1110 | Group A: glucomannan + rifaximin 400 mg bid for 7 days each month.<br>Group B: glucomannan | Group A: 63.9% reduction of the symptom score as compared to 47.6% in patients of Group B at 12 months ($p < 0.001$). |
| Papi et al.[101] | 1995 | RCT | 168 SUDD<br>• Group A: 84<br>• Group B: 84 | Group A: glucomannan 2 g/day + rifaximin 400 mg bid for 10 d/month.<br>Group B: glucomannan 2 g/day + placebo for 10 d/month. | Group A: 68.8% symptom-free or mild symptoms at 12 months ($p = 0.001$). |
| Latella et al.[103] | 2003 | Open RT | 968 SUDD<br>• Group A: 558<br>• Group B: 346 | Group A: glucomannan 4 g/day + rifaximin 400 mg bid + for 7 d/month.<br>Group B: glucomannan 4 g/day. | Group A: 56.5% symptom-free at 12 month ($p < 0.001$) and fewer reoccurrence of acute diverticulitis ($p = 0.05$). |
| Colecchia et al.[104] | 2007 | Open RT | 307 SUDD<br>• Group A: 184<br>• Group B: 123 | Group A: rifaximin 400 mg bid for 7 day/month + fiber supplementation (>20 g/day)<br>Group B: fiber supplementation (>20 g/day). | Group A had greater reduction in symptomatic score ($p < 0.001$) with higher probability of symptom reduction ($p < 0.0001$) and lower complication frequency ($p < 0.028$). |
| Festa et al.[107] | 2017 | Retrospective cohort study | 124 with diverticular disease and at least 1 past episode of acute diverticulitis<br>• Group A: 72<br>• Group B: 52 | Group A: rifaximin 400 mg bid for 10 d/month.<br>Group B: Mesalazine 2400 mg/day | Lower recurrence of acute diverticulitis in the Rifaximin group ($p = 0.015$). |
| Di Mario et al.[102] | 2019 | Retrospective cohort study | 816 SUDD, 8-year follow-up<br>• Group A: 346<br>• Group B: 470 | Group A: rifaximin 800 mg/day for 7 days/month.<br>Group B: any other drug on demand. | Group A had significant relief of symptoms ($p < 0.000$) at 8-year follow-up. No significant difference in prevention of acute diverticulitis. |

Abbreviations: *n*, number; RCT, randomized controlled trial; SUDD, symptomatic uncomplicated diverticular disease.

carried out evaluating the clinical efficacy of rifaximin in patients with diverticular disease, still insufficient data are available to establish the real impact on gut microbial environment and its relationship with clinical response.

### 5.4 | Mesalazine

Mesalazine (5-ASA) is a poor-absorbable anti-inflammatory drug derived from sulfasalazine.[109] It is able to inhibit molecular mediators of inflammatory cascades by activating PPAR-$\gamma$ and blocking expression of NF-kB, cyclo-oxygenase, IL-1, thromboxane synthetase, and platelet activating factor.[110,111] Mesalazine can affect intestinal microbiome in different ways through its antibacterial activity with inhibition of expression of bacterial genes involved in invasiveness, epithelial adherence, proliferation, and antibiotic resistance.[22] In particular, the intestinal conversion of mesalazine in acetylsalicylic acid can decrease luminal pH creating a good environment for the growth of *Lactobacilli* and *Bifidobacteria*, which have anti-inflammatory properties.[112] Moreover, mesalazine can reduce the anoxic environment typical of some inflammatory diseases by inhibiting COX-2 expression and free radicals production, thus promoting eubiosis.[113] In addition, it is able to mitigate the destruction of epithelial tight junctions and to decrease intestinal permeability by inhibiting pro-inflammatory cytokines expression, thus strengthening the gut barrier function.[114] Finally, in vitro experiments found that mesalazine can directly affect the microbiome by inhibiting several pathological bacterial species such as *Mycobacterium avium paratuberculosis* and *Salmonella enterica typhimurium*.[113] It is also likely that other bacterial species could be affected by mesalazine, but further research is needed to understand how this drug can modulate microbiota in humans in real life.

From a clinical point of view, the usefulness of mesalazine in diverticular disease is still unclear (Table 5). Despite mesalazine has been reported to be effective in reducing abdominal symptoms in SUDD, either alone or combined to a probiotic,[115,116] other studies failed to report a significant improvement of this outcome.[117] In patients with SUDD, the cyclic administration of mesalazine was more effective in reducing symptom scores compared to the administration of rifaximin alone; higher dosage of mesalazine (800 mg bid vs. 400 mg bid) showed greater symptom relief.[118] Specifically, a daily mesalazine administration showed better results compared to a cyclic regimen in reducing symptoms and in the primary prevention of acute diverticulitis in 86 SUDD patients.[119] Although two systematic reviews showed that mesalazine was able to reduce symptom burden and first diverticulitis occurrence in SUDD patients,[120,121] a more recent meta-analysis highlighted no differences between placebo and mesalazine in symptom control and acute diverticulitis prevention.[122]

In patients with recurrent diverticulitis, mesalazine combined to rifaximin was more effective than rifaximin alone in reducing abdominal symptoms, improving bowel habit and preventing re-occurrences.[123] Unfortunately, well-performed randomized controlled trials (PREVENT 1 and PREVENT 2, principally) showed that mesalamine was not superior to placebo in preventing recurrent diverticulitis.[117,124,125]

In conclusion, scant data are available on the clinical efficacy of mesalazine in diverticular disease and even less on its impact on the gut microbiota of these patients.

### 5.5 | Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) refers to the procedure of transferring fecal bacteria and other microbes from a healthy individual into a patient, in order to restore eubiosis.[126] Intestinal microbiota samples can be introduced through the lower gastrointestinal tract via colonoscopy or enema, or through the upper gastrointestinal tract in capsules or via a nasogastric-tube.[127] Although the main indication of FMT is the treatment of refractory *Clostridium difficile* infection,[126] new applications are being explored such as for the treatment of IBD, IBS, autism, obesity, or hepatic encephalopathy.[128]

Following FMT, the recipient microbiota enriches in abundance of *Bacteroides* and *Firmicutes* in a proportion similar to that of the healthy donor microbiota.[129] Recipient shifts to a donor-like microbiota within one-two days and remains comparable to that of donors until 6–12 months.[130] From a metabolomic prospective, it has been suggested that FMT promotes a shift in bacterial species capable of metabolizing bile acids, such as *Clostridium cl. XIVa*.[131] Given this rationale for FMT and the upcoming evidences on a beneficial effect of gut microbiota modulation in patients with diverticular disease, Meyer et al. successfully administered for the first time FMT to a patient suffering from multiple, recurrent and multifocal episodes of acute diverticulitis, obtaining a complete remission of symptoms after a 20-month follow-up.[132] On the contrary, this isolate report should be sided by a case report of acute diverticulitis onset 2 h after hospital discharge for *Clostridium difficile* infection treated by FMT et al.[133] If FMT may represent, a novel therapeutic approach for DD remains to be demonstrated in ad hoc studies.

## 6 | CONCLUSION

Although the etiopathogenesis of diverticula occurrence and symptom development is still not well understood, dysbiosis seems to play a central role. Therefore, targeting gut microbiota by restoring its quality and quantity represents one of the cornerstones in the management of diverticular disease. Probiotics or rifaximin with or without fiber supplementation have been shown to be effective in reducing symptoms of SUDD. The effectiveness of these treatments in the prevention of acute or recurrent diverticulitis remains unsettled. Additional randomized controlled trials are needed to understand microbial shifts following different therapeutic strategies,

**TABLE 5** Main studies reporting on Mesalazine administration in diverticular disease.

| Author | Year | Study | Patients (n) and disease | Therapy | Outcome |
|---|---|---|---|---|---|
| Tursi et al.[123] | 2002 | Open RT | 218 recurrent diverticulitis<br>• Group A: 109<br>• Group B: 109 | Group A: rifaximin 400 mg bid + Mesalazine 800 mg tid for 7 days then rifaximin 400 mg bid + Mesalazine 800 mg tid for 7 days/month.<br>Group B: rifaximin 400 mg bid then rifaximin 400 mg bid for 7 days/month. | Group A improved grade of symptoms, bowel habits and reduced reoccurrence of acute diverticulitis ($p < 0.0005$ and $p < 0.0001$ and $p < 0.005$ at 12 months). |
| Brandimarte et al.[115] | 2004 | Open | 86 SUDD | Mesalazine 2.4 g/day + rifaximin 800 mg/day for 10 days, followed by Mesalazine 1.6 g/day for 8 weeks. | Total symptom score decreased vs. baseline score ($p < 0.001$). |
| Tursi et al.[116] | 2006 | Open RT | 85 SUDD:<br>• Group M: 27<br>• Group L: 29<br>• Group ML: 29 | Group M: Mesalazine 1.6 g/day<br>Group L: *L. casei* DG 16 billion/day for 15 day/month.<br>Group ML: Mesalazine 1.6 g/day + *L. casei* DG 16 billion/day for 15 days/month | Mesalazine + probiotic was more effective than Mesalazine or probiotic alone in achieving symptom control ($p = 0.05$). |
| Tursi et al.[119] | 2007 | Open RT | 34 SUDD:<br>• Group A: 18<br>• Group B: 16 | Group A: Mesalazine 1.6 g/day<br>Group B: Mesalazine 1.6 g/day 10 days per month. | Daily supplying of Mesalazine seemed more effective in symptom control ($p = 0.05$) and in prevention of recurrence of symptoms ($p < 0.005$). |
| Comparato et al.[118] | 2007 | Open RT | 268 SUDD patients<br>• Group R1: 66<br>• Group R2: 69<br>• Group M1: 67<br>• Group M2: 66 | Group R1: rifaximin 200 mg bid<br>Group R2: rifaximin 400 mg bid<br>Group M1: Mesalazine 400 mg bid<br>Group M2: Mesalazine 800 mg bid<br>Therapy for 10 day/month | Group M2 showed lower frequency of abdominal symptoms. Overall, patients from Groups M1 and M2 had greater symptom relief compared to rifaximin groups. |
| Gatta et al.[125] | 2012 | Open RT | 149 SUDD<br>• Group M: 67<br>• Group C: 82 | Group M: Mesalazine 800 mg bid for 10 days/month for 60 months.<br>Group C: no Mesalazine. | Mesalazine did not significantly reduce incidence of acute diverticulitis. |
| Parente et al.[138] | 2013 | RCT | 92 post-acute diverticulitis<br>• Group A: 45<br>• Group B: 47 | Group A: Mesalazine 800 mg bid for 10 days/month for 24 months.<br>Group B: placebo for 24 months. | Mesalazine improved acute diverticulitis re-occurrence but not significantly. Mesalazine significantly improved QoL and physical condition. |
| Raskin et al.[124] | 2014 | RCT | 1182 with past episode of AD<br>• PREVENT 1: 590<br>• PREVENT 2: 592 | PREVENT 1: Mesalazine 1.2–2.4-4.8 g/day or placebo for 104 weeks<br>PREVENT 2: Mesalazine 1.2–2.4-4.8 g/day or placebo for 104 weeks | Mesalazine did not reduce significantly time to recurrence of AD |
| Kruis et al.[117] | 2017 | RCT | 675 post-AD<br>• SAG-37: 345<br>• SAG-51: 330 | SAG-37: Mesalazine 3 g/day or placebo<br>SAG-51: Mesalazine 1.5–3 g/day or placebo | Mesalazine is not superior to placebo in preventing re-occurrence of AD. |

Abbreviations: AD, acute diverticulitis; *n*, number; RCT, randomized controlled trial; SUDD, symptomatic uncomplicated diverticular disease.

including fecal microbiota transplantation, in symptom control and acute diverticulitis prevention.

## AUTHOR CONTRIBUTIONS

GM, FB, and GB designed the review; GM, FB, CC, and MRB performed the literature search, study selection, and data extraction; GM and FB drafted the paper; VS and GB critically reviewed the paper; all authors approved the final version of the manuscript.

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No competing interests declared.

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