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Intestinal microbiota, low-grade inflammation and probiotic modulation in symptomatic uncomplicated diverticular disease: experimental and clinical perspectives. A narrative review

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Abstract

Symptomatic Uncomplicated Diverticular Disease (SUDD) of the colon represents one of the most common gastrointestinal disorders in Western countries, with prevalence increasing significantly with age. Among its clinical manifestations, SUDD is characterized by recurrent abdominal pain, bloating, and alterations in bowel habits in the absence of overt inflammatory complications.

Although the pathogenesis of diverticular disease has traditionally been attributed to mechanical factors such as increased intraluminal pressure and structural weakness of the colonic wall, growing evidence suggests that intestinal dysbiosis and low-grade mucosal inflammation play a crucial role in the development of symptoms. Alterations in gut microbiota composition may disrupt epithelial barrier integrity, promote inflammatory signaling pathways, and contribute to visceral hypersensitivity. In recent years, probiotics and symbiotic formulations have been investigated as potential therapeutic strategies aimed at restoring intestinal microbial equilibrium and modulating inflammatory responses. This mini-review summarizes the current knowledge regarding the pathophysiology of SUDD, with particular emphasis on microbiota-host interactions, and discusses the experimental and clinical evidence supporting the use of probiotics in the management of SUDD.

Introduction

Symptomatic Uncomplicated Diverticular Disease (SUDD) of the colon is highly prevalent in industrialized countries and represents a major cause of gastrointestinal morbidity and healthcare utilization. Epidemiological studies indicate that the prevalence of diverticulosis increases markedly with age, affecting more than half of individuals over the age of sixty in Western populations.¹ Although most individuals with diverticula remain asymptomatic, approximately 10–25% of patients develop clinical manifestations ranging from chronic symptoms to acute inflammatory complications.²

The clinical spectrum of diverticular disease includes asymptomatic diverticulosis, SUDD, and acute diverticulitis with or without complications. SUDD represents a clinical entity characterized by persistent abdominal pain, bloating, and changes in bowel habits in patients with diverticula but without evidence of acute inflammation or structural complications.³ For decades, the pathogenesis of SUDD was primarily explained by mechanical factors such as increased intraluminal pressure, low dietary fiber intake, and structural weaknesses of the colonic wall. However, this model does not fully explain the occurrence of symptoms in patients with otherwise uncomplicated diverticula.

Recent advances in microbiome research have highlighted the importance of interactions between the intestinal microbiota, mucosal immune system, and enteric nervous system in gastrointestinal

disorders. In this context, increasing evidence suggests that alterations in gut microbiota composition and function may play a central role in the pathophysiology of SUDD (Figure 1).⁴

Methodological approach

A comprehensive literature search was conducted across electronic databases, including PubMed, Scopus, and Google Scholar, to identify relevant studies published up to 2025. The search strategy employed keywords such as "diverticular disease," "SUDD," "gut microbiota," and "probiotics." We included experimental studies, clinical trials, and systematic reviews focusing on the pathophysiological role of dysbiosis and the therapeutic efficacy of probiotic supplementation. Articles were selected based on their relevance to the interaction between microbiota-host homeostasis and low-grade inflammation in the context of SUDD.

Pathophysiology of diverticular disease

Colonic diverticula are sac-like protrusions of the mucosa and submucosa through weak points in the muscular layer of the colon. They can be non-inflamed or inflamed (Figure 2) and may present abscess or be inverted (Figure 3). Sometimes, when sectioned, they may present wall thickening (Figure 4). Overall, these structural weaknesses are typically located at sites where blood vessels penetrate the muscular wall. Several factors contribute to the formation of diverticula, including aging-related connective tissue changes, reduced dietary fiber intake, increased intraluminal pressure, obesity, and sedentary lifestyle.⁵

However, the presence of diverticula alone does not necessarily result in symptoms. Many individuals with diverticulosis remain asymptomatic throughout their lifetime, suggesting that additional factors are involved in the development of symptomatic disease. Among the mechanisms proposed to explain symptom generation in SUDD are: alterations in colonic motility; visceral hypersensitivity; low-grade mucosal inflammation; and changes in intestinal microbiota composition.⁶ Visceral hypersensitivity has been proposed as an important factor contributing to abdominal pain in patients with SUDD. Similar mechanisms have been described in other gastrointestinal disorders such as irritable bowel syndrome.⁷

In addition, several studies have reported evidence of mild inflammatory changes in the colonic mucosa of patients with SUDD, including increased infiltration of immune cells and elevated levels

of inflammatory mediators.⁸ These findings support the hypothesis that chronic low-grade inflammation may contribute to symptom generation.

Experimental evidence

Basic research and animal models have demonstrated that alterations in the enteric nervous system and colonic motility are primary drivers of diverticular formation.⁹ Experimental studies on mucosal tissues show that low-grade inflammation involves increased infiltration of immune cells and elevated cytokines, suggesting a biological basis for chronic symptoms.⁸

Clinical observations

In clinical practice, patients with SUDD frequently report visceral hypersensitivity, a mechanism similar to that observed in irritable bowel syndrome. Clinical imaging and biopsies from patients have confirmed that structural weaknesses and mucosal changes are often accompanied by these sensory alterations.⁹

The role of gut microbiota in intestinal homeostasis

The human gastrointestinal tract hosts a complex microbial ecosystem composed of trillions of microorganisms belonging to hundreds of bacterial species. This microbial community plays a fundamental role in maintaining intestinal homeostasis and contributes to several physiological processes including digestion, metabolism, and immune regulation. Among the most important functions of the gut microbiota are the fermentation of dietary fibers, the production of short-chain fatty acids, the regulation of epithelial barrier integrity, and the modulation of mucosal immune responses.¹⁰

Short-chain fatty acids, particularly butyrate, are key metabolites produced by bacterial fermentation of dietary fibers. These molecules provide energy for colonocytes and exert anti-inflammatory effects by regulating immune signaling pathways and epithelial cell function.⁹ Disruption of the normal balance of the microbiota, commonly referred to as dysbiosis, has been implicated in a variety of gastrointestinal disorders, including inflammatory bowel disease, irritable bowel syndrome, and colorectal cancer.¹¹

Dysbiosis and low-grade inflammation in diverticular disease

Growing evidence suggests that alterations in gut microbiota composition may contribute to the development of SUDD and its clinical manifestations. Several studies have reported differences in the microbial profiles of patients with diverticular disease compared with healthy individuals.¹² These alterations may include reduced microbial diversity and changes in the relative abundance of specific bacterial taxa.⁴

Recent evidence highlights that the gut microbiota in SUDD patients is strictly associated with the clinical phenotype, specifically stratifying according to the severity of abdominal pain.¹² Multi-omics analyses have identified a distinct microbial signature in patients with high pain scores, characterized by an enrichment of Streptococcaceae and a concomitant reduction in beneficial taxa such as *Bifidobacterium* sp. and *Dorea* sp.⁵

Dysbiosis may lead to the production of pro-inflammatory metabolites and bacterial components capable of activating the mucosal immune system.¹³ One important consequence of microbial imbalance is the disruption of epithelial tight junctions, resulting in increased intestinal permeability. Increased permeability allows bacterial products such as lipopolysaccharides to cross the epithelial barrier and interact with immune cells in the lamina propria. Activation of innate immune receptors may then trigger the production of cytokines and chemokines, promoting chronic low-grade inflammation.¹⁴ This inflammatory environment may contribute to the development of abdominal pain, altered bowel habits, and other symptoms associated with SUDD.

Interplay between microbial dysbiosis and clinical symptomatology

The transition from asymptomatic diverticulosis to the clinical phenotype of SUDD appears to be governed by a multifaceted biological crosstalk where dysbiosis serves as the initial catalyst. Environmental factors and diet drive intestinal dysbiosis, compromising epithelial barrier integrity. The resulting permeability allows bacterial translocation, triggering mucosal immune activation and chronic low-grade inflammation. These processes contribute to visceral hypersensitivity, altered motility, and typical SUDD symptoms. Probiotics may counteract these events by restoring microbial balance, enhancing barrier function, and reducing inflammation. A reduction in commensal diversity, coupled with the expansion of pro-inflammatory taxa, compromises the mucous layer and epithelial tight junction integrity. This loss of barrier function facilitates the translocation of bacterial components into the lamina propria, triggering a persistent recruitment of immune cells and the subsequent release of inflammatory mediators. Such a localized inflammatory

milieu is not merely a bystander effect but acts as a direct irritant to the enteric nervous system, promoting the visceral hypersensitivity frequently observed in these patients. Consequently, the overarching symptoms of SUDD ranging from bloating and altered motility to recurrent abdominal pain can be viewed as the macroscopic expression of this underlying microscopic disruption of intestinal homeostasis.

Probiotics as modulators of intestinal microbiota

Probiotics are defined as live microorganisms that confer health benefits to the host when administered in adequate amounts.¹⁵ The most commonly studied probiotic organisms belong to the genera *Lactobacillus* and *Bifidobacterium*.

The beneficial effects of probiotics are mediated through several biological mechanisms affecting both microbial communities and host physiology. Probiotic microorganisms may compete with pathogenic bacteria for adhesion sites and nutrients within the intestinal lumen. By promoting the growth of beneficial commensal bacteria, they contribute to the restoration of microbial equilibrium. In addition, several probiotic strains have been shown to enhance the integrity of epithelial tight junctions, thereby improving barrier function and reducing intestinal permeability.¹⁴ The commercial formulation commonly proposed for supplementation comprised high-concentration probiotics and prebiotics, including *Lactobacillus plantarum* LP115 (400 MLD/g), *Lactobacillus rhamnosus* LR32 (200 MLD/g), *Bifidobacterium bifidum* SGB02 (10 MLD/g), fructooligosaccharides (FOS), inulin, maltodextrin, *Lactobacillus acidophilus* LA02 (100 MLD/g), silicon dioxide, and magnesium stearate.¹⁶

Probiotics may also modulate immune responses by influencing cytokine production and regulating the activity of immune cells in the gut-associated lymphoid tissue. These effects may contribute to the attenuation of chronic low-grade inflammation within the intestinal mucosa.¹⁶ Finally, many probiotic microorganisms produce metabolites such as short-chain fatty acids that exert protective and anti-inflammatory effects on intestinal epithelial cells.¹⁶

Clinical evidence for probiotics in symptomatic uncomplicated diverticular disease

The potential role of probiotics in the management of SUDD has been investigated in several clinical studies over the past two decades.¹⁷ Although some studies have reported improvements in gastrointestinal symptoms such as abdominal pain and bloating,¹⁷ the available clinical evidence

remains significantly heterogeneous and limited. Many existing studies are characterized by small sample sizes, observational designs, or a lack of standardized protocols, which constrains the generalizability of the findings.¹⁸

The rationale for probiotic therapy in SUDD is based on the hypothesis that restoring microbial balance may reduce mucosal inflammation and improve epithelial barrier function (Table 1). Some investigations have also explored the combined use of probiotics and anti-inflammatory agents such as mesalazine (5-aminosalicylic acid). This approach aims to target both microbial dysbiosis and mucosal inflammation simultaneously.¹⁸

Preliminary findings suggest that combination therapies may provide greater symptomatic improvement compared with pharmacological therapy alone, although the available studies are limited by small sample sizes and methodological variability.¹⁸ It is crucial to emphasize that the efficacy of probiotics is highly strain-specific; therefore, results obtained with one formulation cannot be automatically extrapolated to others without rigorous comparative trials.

Consequently, larger randomized controlled trials are required to determine the efficacy of specific probiotic strains and to establish standardized treatment protocols.¹⁸

Experimental perspectives and emerging research

Recent advances in molecular biology and microbiome research have significantly improved our understanding of host-microbiota interactions. High-throughput sequencing technologies, including 16S rRNA gene sequencing, allow detailed characterization of microbial communities and their functional properties.¹¹

These techniques may help identify microbial signatures associated with disease severity and therapeutic response in patients with SUDD. Future research should aim to integrate microbiome analysis with metabolomic and immunological studies in order to better understand the biological mechanisms underlying diverticular disease. In particular, the identification of specific microbial metabolites involved in inflammatory signaling pathways may open new therapeutic perspectives.¹⁹

Conclusions

Accumulating evidence indicates that intestinal microbiota alterations and low-grade mucosal inflammation play a central role in the pathophysiology of symptomatic uncomplicated diverticular

disease. Modulation of the gut microbiota through probiotic supplementation represents a promising strategy for restoring intestinal homeostasis and improving gastrointestinal symptoms.

Although preliminary clinical data suggest potential benefits, further well-designed randomized controlled trials are required to determine the optimal probiotic strains, dosages, and treatment regimens. In fact, while probiotic supplementation represents a theoretically sound strategy for restoring intestinal homeostasis, its routine clinical application in SUDD is currently hindered by the lack of high-quality, large-scale randomized controlled trials.

A deeper understanding of the complex interactions between gut microbiota, epithelial barrier function, and mucosal immune responses will likely contribute to the development of innovative microbiota-based therapeutic strategies for SUDD.

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Table 1. Proposed biological mechanisms through which probiotic microorganisms may influence the pathophysiology of diverticular disease. These mechanisms include modulation of intestinal microbiota composition, improvement of epithelial barrier integrity, immunomodulatory activity, metabolic effects related to short-chain fatty acid production, and the modulation of neural signaling pathways involved in visceral sensitivity and intestinal motor function.

Mechanism	Biological effects	Potential clinical impact	Supporting References
Microbiota modulation	Competition with pathogenic bacteria and restoration of commensal microbial populations	Improved microbial balance	[13,17]
Enhancement of epithelial barrier	Increased expression of tight junction proteins and reduced intestinal permeability	Protection against bacterial translocation	[14,17]
Immunomodulation	Regulation of cytokine production and immune cell activation	Reduction of mucosal inflammation	[9]
Metabolic activity	Production of short-chain fatty acids such as butyrate	Improved epithelial health and anti-inflammatory effects	[4,19]
Neural and Motor modulation	Interaction with the enteric nervous system and visceral signaling pathways	Possible reduction of visceral hypersensitivity and normalization of colonic motility	[7,8]

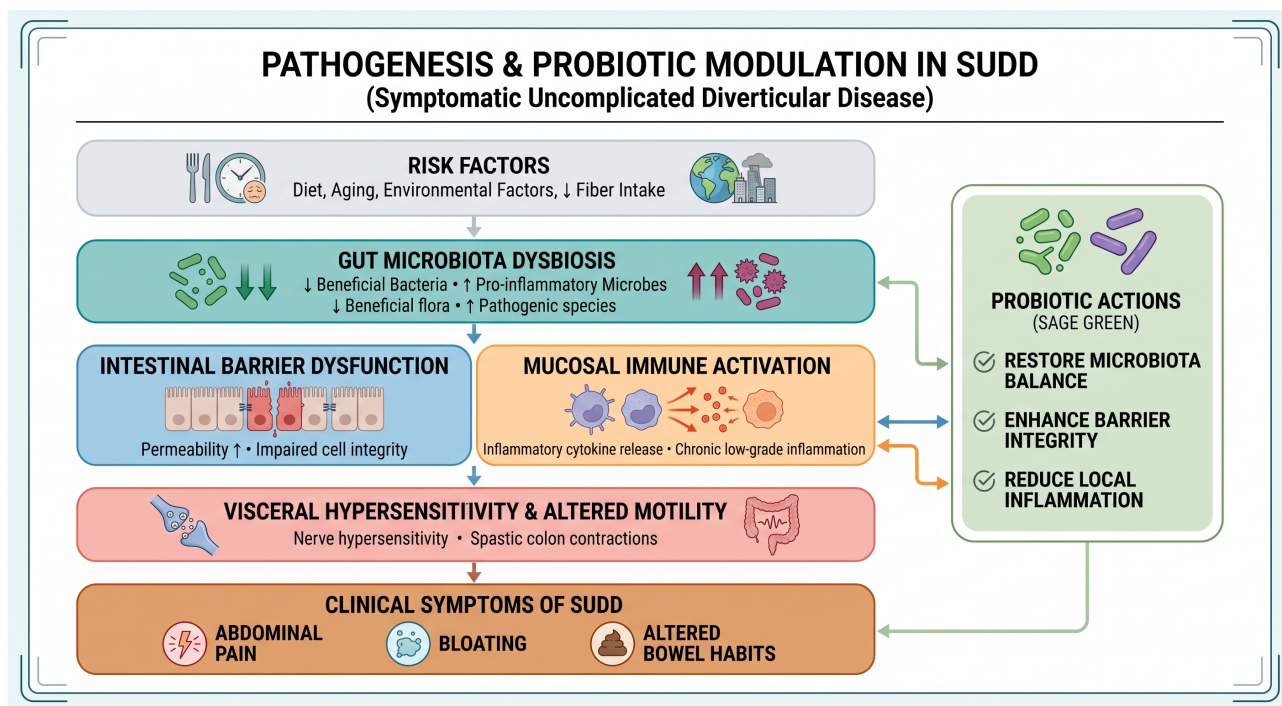
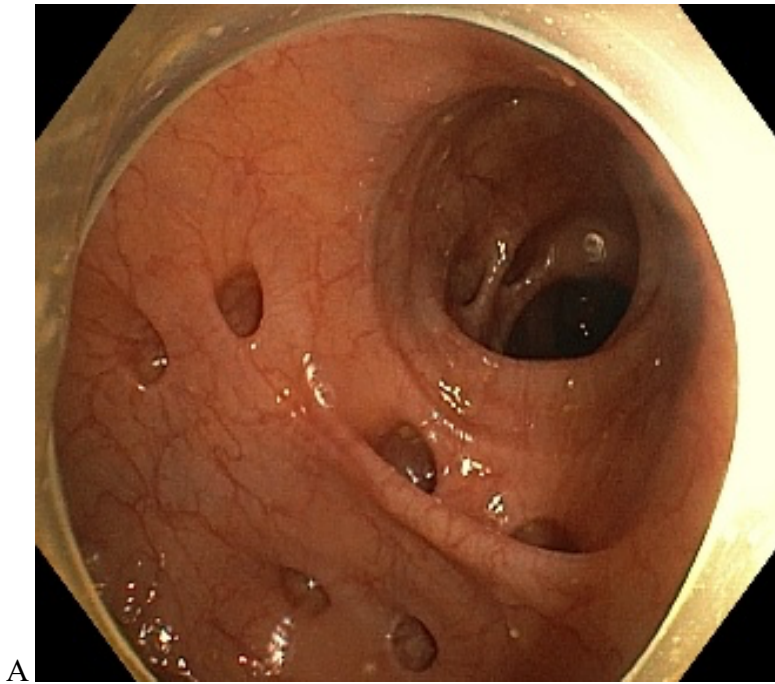
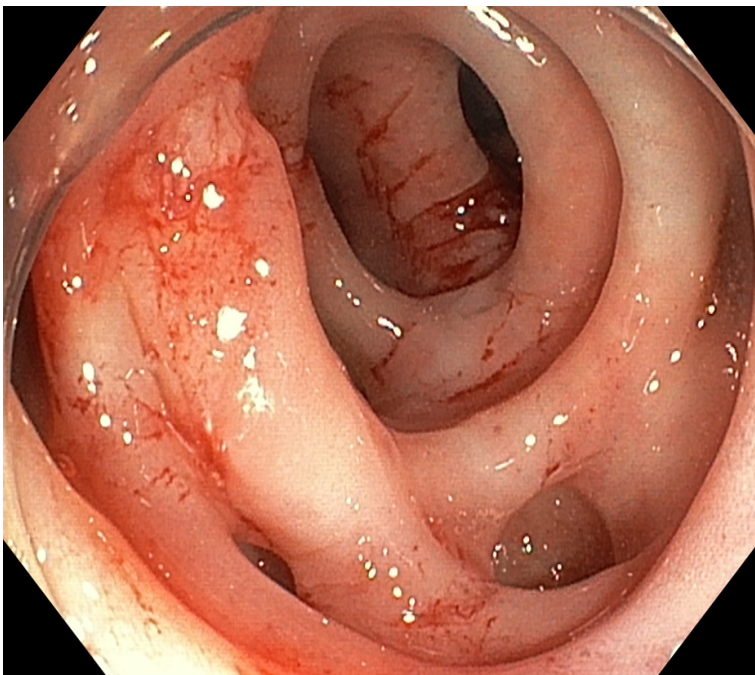


Figure 1. Gut microbiota dysbiosis and probiotic modulation in symptomatic uncomplicated diverticular disease (SUDD). This schematic illustration summarizes the proposed pathophysiological mechanisms linking intestinal microbiota alterations to the development of symptoms in SUDD, as well as the potential modulatory effects of probiotic therapy. Figure 1 was obtained using Inkscape.

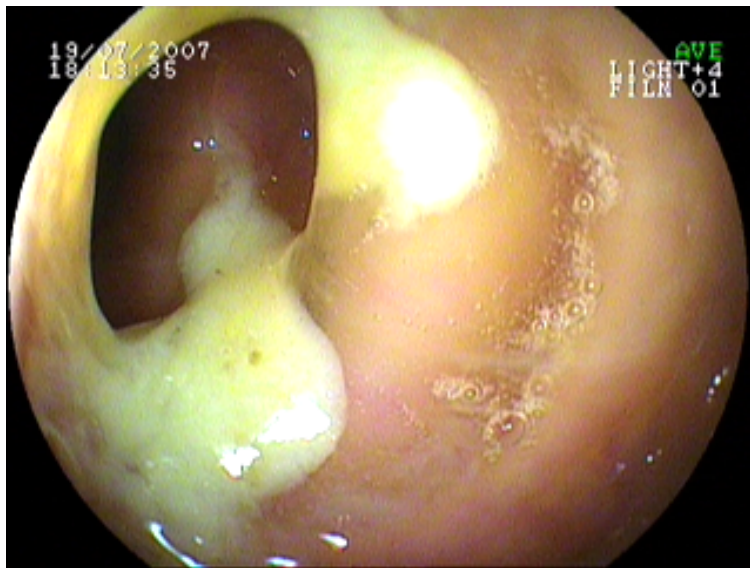


A



B

Figure 2. Endoscopic photographic image of multiple non-inflamed (A) and inflamed (B) sigmoid diverticula. The photos were personally obtained by one of the authors (GT, Italy).



A



B

Figure 3. Endoscopic presentation of acute diverticular complications. A) A single, severely inflamed colonic diverticulum exhibiting localized mucosal erythema and edema, accompanied by a peridiverticular abscess and purulent exudate adhering to the neck of the pouch; B) An inverted diverticulum mimicking a sessile polypoid lesion; careful inspection reveals a pliable structure that can be easily depressed with the biopsy forceps, distinguishing it from true epithelial neoplasia. The photos were personally obtained by one of the authors (MCS, Brazil)

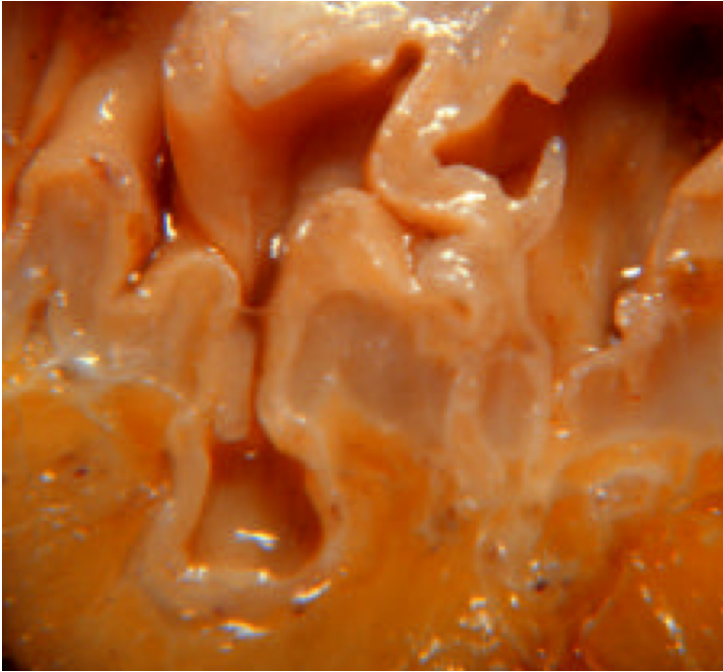


Figure 4. Appearance of wall thickening (sectioned) in chronic diverticular disease. The photo was personally obtained by one of the authors (MCS, Brazil).

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