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Rifaximin as a Therapeutic Ally in the Modulation of Dysbiosis: A Narrative Review of Its Applicability in Gastrointestinal Disorders

Joana Frias[a, b] Miguel Martins[a, b] Armando Peixoto[a, b, c] Guilherme Macedo[a, b, c]

[a]Department of Gastroenterology, São João University Hospital, Porto, Portugal; [b]WGO Gastroenterology and Hepatology Training Center, Porto, Portugal; [c]Faculty of Medicine of University of Porto, Porto, Portugal

Keywords
Rifaximin · Dysbiosis · Microbiome

Abstract

Background: The gastrointestinal microbiota is vital for a well-functioning digestive tract, nutrient metabolism, immune support, and protection against pathogenic microorganisms. Disruption of this balance is known as dysbiosis. Rifaximin, an oral antibiotic with selective action, reduces harmful gut bacteria while preserving beneficial species, aiding in microbiota restoration. ***Summary:*** Alterations in the intestinal microbiota are implicated in many gastrointestinal disorders. Rifaximin, by targeting and modulating the microbiota, may serve as a powerful tool in the approach of these conditions. ***Key Messages:*** This narrative review summarizes the main uses of rifaximin in gastrointestinal disorders like irritable bowel syndrome, diverticular disease, small intestinal bacterial overgrowth, traveler's diarrhea, hepatic encephalopathy, *Clostridioides difficile* infection, and inflammatory bowel disease.

Rifaximina como Aliado Terapêutico na Modulação da Disbiose: Revisão Narrativa da Sua Aplicabilidade em Patologias do foro Gastrointestinal

Palavras Chave
Rifaximina · Disbiose · Microbioma

Resumo

Contexto: O microbioma gastrointestinal é essencial para o bom funcionamento do trato digestivo, metabolismo de nutrientes, suporte imunológico e proteção contra microorganismos patológicos. A disrupção desse equilíbrio é chamada de disbiose. A rifaximina, um antibiótico oral de ação seletiva, reduz a quantidade de bactérias nocivas do intestino e preserva as benéficas, auxiliando na restauração do microbioma. ***Sumário:*** Alterações no microbioma intestinal estão implicadas em muitas patologias do foro gastrointestinal. A rifaximina, ao atuar na modulação do microbioma, pode servir como uma poderosa ferramenta

Joana Frias and Miguel Martins contributed equally to this work.

karger@karger.com
www.karger.com/pjg

Correspondence to:
Armando Peixoto, armandoafp5@gmail.com

na abordagem destas condições. ***Mensagens-chave:*** Esta revisão narrativa resume os principais usos da rifaximina em distúrbios gastrointestinais como Síndrome do Intestino Irritável, Doença Diverticular, Sobrecrescimento Bacteriano do Intestino Delgado, Diarreia do Viajante, Encefalopatia Hepática, Infeção por *Clostridioides difficile* e Doença Inflamatória Intestinal.

Introduction

The gastrointestinal (GI) microbiota is a complex and dynamic ecosystem comprising a diverse array of microorganisms, including bacteria, archaea, viruses (bacteriophages), fungi (mycobiome), and even protozoa in some environments [1, 2]. This microbial community is essential for maintaining a well-functioning digestive tract, contributing to nutrient metabolism, supporting immune functions, and protecting against pathogenic microorganisms [3]. As shown in Figure 1, more than 90% of the human gut microbiota is composed of four major phyla: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. Additionally, a small portion of Fusobacteria and the other minor phyla contribute to the remaining diversity [4].

Dysbiosis refers to an imbalance in the gut microbiota, where the composition and function of the microbial community are disrupted [5]. This imbalance can manifest as an overgrowth of pathogenic bacteria, a reduction in beneficial species, or a decrease in overall microbial diversity [5]. Such alterations can lead to a pro-inflammatory state, increased gut permeability, and elevated oxidative stress, which are implicated in the pathogenesis of various digestive disorders [6]. Conditions such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), small intestinal bacterial overgrowth (SIBO), and hepatic encephalopathy (HE) are often associated with dysbiotic shifts in the gut microbiota.

Rifaximin, a nonabsorbable antibiotic that acts primarily within the GI tract plays a crucial role in modulating dysbiosis. Its mechanism of action involves the inhibition of bacterial RNA synthesis by attachment to the β-subunit of bacterial DNA-dependent RNA polymerase, inhibiting transcription [7]. By targeting a broad spectrum of bacteria, it reduces the pathogenic bacterial load in the gut while sparing beneficial species [8]. This selective antimicrobial action helps restore a balanced gut microbiota; alleviating symptoms associated with dysbiosis [9]. Rifaximin also exhibits anti-inflammatory properties, potentially by reducing intestinal inflammation mediated by bacterial endotoxins [10]. Rifaximin's low systemic absorption minimizes the risk of systemic side effects, making it an ideal candidate for long-term management of conditions like IBS and HE [11]. By modulating the gut microbiota, rifaximin not only addresses the symptoms of these disorders but also targets their underlying microbial imbalances, offering a comprehensive approach to treatment [9].

Antimicrobial resistance to rifaximin cannot be entirely avoided, but the risk appears lower than that of most antibiotics [11]. This is due to rifaximin's low water solubility, which limits its bioavailability in the aqueous intestinal tract, exposing the microbiota to minimal drug concentrations. Additionally, rifaximin's mechanisms of action do not require high drug concentrations, and cross-transmission of resistance between bacterial species is rare [12]. However, the risk must be monitored, particularly with long-term or repeated use, as cases like vancomycin-resistant *Enterococcus* in liver disease patients suggest the need for further investigation [13].

Resistance rates vary by context and population. For example, rifaximin resistance occurs in 34.1% of *Clostridioides difficile* infection (CDI) cases, rising to 84.6% with prior exposure [14]. Although resistance is less common in broader applications, mutations in the bacterial *rpoβ* gene contribute to resistance, particularly with prolonged use [15].

Table 1 provides an overview of microbiota alterations across various digestive pathologies, comparing them to the distribution observed in a healthy population, along with the proposed microbiota-modulating effects of rifaximin. We postulate that rifaximin exerts a selective antimicrobial effect, targeting the overgrowth of pathogenic or pro-inflammatory bacteria (e.g., certain Proteobacteria) while preserving or promoting beneficial microbial populations (e.g., Firmicutes). However, it is important to acknowledge that microbiota composition is highly individual and difficult to define precisely, with percentages varying based on factors such as diet, age, genetics, and environmental influences.

Irritable Bowel Syndrome

IBS is a functional GI disorder characterized by chronic abdominal pain and altered bowel habits [25–27]. The disorder is subtyped based on predominant symptoms: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M), and unsubtyped IBS. The exact etiology remains unclear, but factors such as disturbed gut-brain interactions, motility disturbances, visceral hypersensitivity, and intestinal microbiota

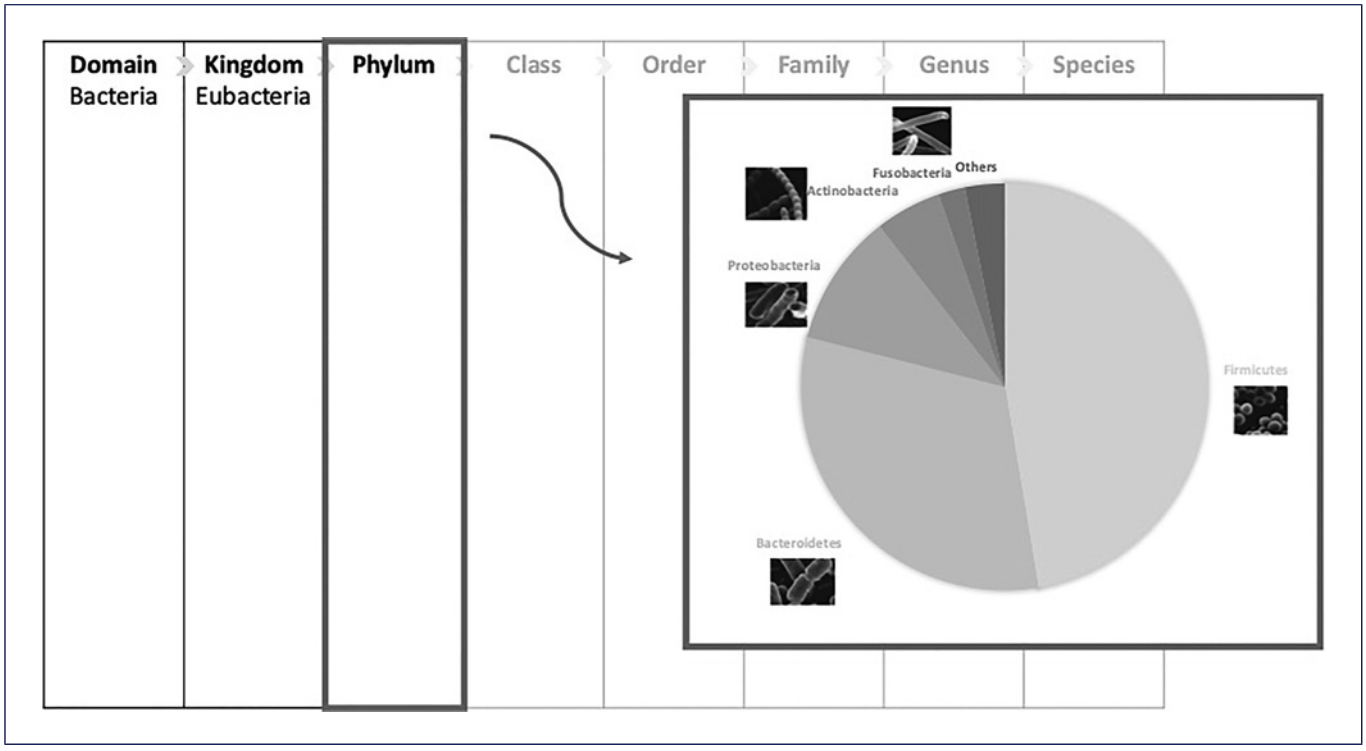

Fig. 1. Schematic representation of major phyla in the human gut microbiome based on Wang et al. [4].

Table 1. Microbiota changes in different digestive pathologies compared to a healthy population, with the proposed mirobiota-modulating effects of rifaximin described at the end

	Firmicutes	Bacteroidetes	Proteobacteria	Actinobacteria	Fusobacteria
Normal population [4]	High abundance (~45%)	High abundance (~30%)	Moderate abundance (~10%)	Low abundance (~5%)	Low abundance (~1–2%)
IBS [16]	↓		↑		
Diverticular disease [17]	↓		↑		
SIBO [18]	↓		↑		
TD [19]	↓		↑		
HE [20, 21]	↓		↑		
CDI [22, 23]	↓		↑	↓	
UC [24]					↑
CD [24]	↓		↑		
Microbiota-modulating postulated effect of rifaximin	↑		↓		

alterations are believed to contribute to its pathophysiology [28]. IBS-D is often associated with a reduced gut bacteria diversity, with increased Proteobacteria and decreased Firmicutes [16].

Rifaximin has been extensively studied for IBS-D (Table 2). It has been shown to provide significant relief from symptoms such as bloating, diarrhea, and abdominal pain. FDA approval was based on large trials

Table 2. Overview of the published work regarding the applications of rifaximin in IBS

Study	Design	Participants	Intervention	Main findings	Conclusion
Pimentel et al. [30] (2006)	Bicentric RCT	87	Rifaximin 400 mg TID, 10 days (compared with placebo)	• ↓ Global symptoms • ↓ Bloating • No effect on diarrhea • No effect of pain	Effective for bloating and global symptoms in IBS following gastroenteritis
Pimentel et al. [31] (2011) (TARGET 1 & 2)	Multicentric RCT	600	Rifaximin 550 mg TID, 2 weeks (compared with placebo)	• ↓ Diarrhea • ↓ Bloating • Unclear on pain	Effective especially for diarrhea and bloating in IBS-D
Menees et al. 2012 [29] (2012)	Meta-analysis of RCT	3,982	Various doses	• ↓ Global symptoms • ↓ Bloating • ↓ Pain	Effective and safe across IBS patients
Lembo et al. [32] (2016) (TARGET 3)	Multicentric RCT	636	Rifaximin 550 mg TID, 2 weeks 4 months after first treatment (compared with placebo)	• ↓ Diarrhea + Bloating	Effective for relapsing IBS-D

RCT, randomized controlled trial; TID 3 times daily or ter in die.

(TARGET 1 and 2) where a 14-day course of rifaximin at a dose of 550 mg 3 times daily significantly reduced the severity of IBS symptoms, with effects persisting for up to 10 weeks posttreatment. A meta-analysis of 19 randomized controlled trials (RCTs) confirmed the efficacy of rifaximin, showing a pooled NNT of 10 for global symptom improvement [29]. This study also demonstrated that rifaximin is well-tolerated, with adverse effects comparable to those of a placebo – the most common side effects including nausea and headaches.

The TARGET 3 study confirmed that rifaximin is safe for repeated use in patients with recurrent symptoms, with similar efficacy and safety profiles across treatment cycles [32]. The recommended treatment course is up to 2 cycles of 14 days each, separated by at least 10 weeks, for recurrent symptoms.

Rifaximin is recommended for IBS-D patients, especially those with moderate-to-severe symptoms [26]. It is not recommended for other IBS subtypes due to insufficient evidence of efficacy [25–27]. Non-pharmacological interventions should be considered first-line therapies alongside rifaximin for comprehensive management [25].

Rifaximin shows promise in treating other disorders of gut-brain interaction beyond IBS, particularly abdominal distension/bloating and functional dyspepsia. Regarding abdominal distension/bloating, a meta-analysis of nine studies involving 3,326 patients with functional GI disorders found that rifaximin significantly improved bloating symptoms (RR 1.22, 95% CI: 1.11–1.35) [33]. However, as the studies included patients with IBS rather than isolating abdominal distension/bloating as per Rome criteria, no definitive conclusions can be drawn about its efficacy in this specific subgroup. Currently, no clinical trials have directly investigated rifaximin's role in abdominal distension/bloating as a standalone diagnosis. For functional dyspepsia, only one RCT has evaluated rifaximin's applicability. The study showed significant improvement in symptoms like belching and postprandial fullness, suggesting potential benefits [34]. However, more research is needed to confirm its efficacy and establish its role in managing functional dyspepsia.

Diverticular Disease

Diverticular disease is a highly prevalent in Western countries, especially among those aged 60 and older. There are several clinical scenarios, ranging from diverticulosis, usually discovered as an incidental finding

during colonoscopy, as most patients remain symptom-free, to acute diverticulitis, which occurs when the diverticula become inflamed or infected [35].

The pathophysiology of acute diverticulitis remains a subject of ongoing debate [35]. Traditionally, the accepted theory suggested that the primary trigger was linked to the blockage of diverticula by a fecalith, potentially resulting in infection. Nevertheless, this is currently considered to be rare. The prevailing theory suggests that chronic, low-grade inflammation plays a crucial role in the disease's pathogenesis. This inflammation may be related to changes in the gut microbiota, such as reduction in beneficial Firmicutes and an increase in harmful Proteobacteria, promoting a pro-inflammatory state [17]. Additional factors, such as visceral hypersensitivity, altered colonic motility and defects in the colonic wall are also considered important [36].

Rifaximin may be used to manage diverticular disease primarily for its ability to modulate gut microbiota and reduce inflammation (Table 3). Evidence suggests its benefits in the management of a specific manifestation of diverticular disease: symptomatic uncomplicated diverticular disease (SUDD). This condition is defined as the coexistence of diverticula and recurrent abdominal pain without visible colonic inflammation. In approximately 4% of cases, SUDD may progress to acute diverticulitis [37]. Combining rifaximin with fiber alleviates symptoms by reducing gut flora proliferation, leading to a decrease in bacterial hydrogen/methane production, by improving fecal bulk due to reduced bacterial degradation of fiber, thereby alleviating pain and potentially accelerating intestinal transit time, consequently reducing constipation [38]. A meta-analysis showed that a 1-year regimen of rifaximin (400 mg twice daily for 7 days/month) plus fiber led to 64.0% of patients becoming symptom-free (pooled rate: 95% CI: 31.4–38.6), compared to 34.9% (95% CI: 60.9–67.0) of patients treated with fiber alone [39]. A retrospective study also found that cyclic rifaximin use provided symptom relief with 47.2% of patients reporting no abdominal pain within 3 months of treatment ($p < 0.001$) [40]. Based on this evidence, various guidelines support rifaximin for SUDD management [41, 42].

Furthermore, the benefits of rifaximin in SUDD seem to extend beyond symptom relief, aiding in both primary and secondary prevention of acute diverticulitis. A meta-analysis showed a 2% lower incidence of acute diverticulitis in SUDD patients treated with rifaximin (400 mg twice daily for 7 days each month over 12 months) plus fiber versus fiber alone ($p = 0.0057$) [39]. More recently, another meta-analysis found that cyclic rifaximin (800 mg daily for 7–10 days/month) reduced the risk of diverticulitis onset by 1.9% and recurrence risk by 24% [49].

There is a final note regarding the use of rifaximin for the prevention of recurrent acute diverticulitis. First, there are studies indicating that its use is ineffective in preventing these episodes [47]. Conversely, other studies suggest benefits in utilizing this antibiotic [46, 48]. From a pathophysiological perspective, its use appears plausible: repeated oral administration of an antibiotic that achieves high concentrations within the GI lumen may significantly impact the intestinal microbiota. However, the evidence is not sufficiently robust to definitively confirm or exclude the use of rifaximin for the prevention of acute diverticulitis episodes in patients with a history of this condition. Therefore, the most recent guidelines do not recommend its use [50].

Small Intestinal Bacterial Overgrowth

SIBO is characterized by an excessive bacterial population in the small intestine, leading to symptoms such as bloating, diarrhea, and malabsorption. The condition is diagnosed based on clinical symptoms and confirmed via breath tests or jejunal aspirate cultures [51].

SIBO involves an overgrowth of facultative anaerobes and a higher concentration of bacteria, such as Proteobacteria, which are less common in a healthy small intestine [52]. The overgrowth can lead to the deconjugation of bile acids, fat malabsorption, and mucosal inflammation.

Rifaximin's nonsystemic nature and broad-spectrum antimicrobial activity make it an effective treatment for SIBO. A systematic review with meta-analysis showed a 70.8% overall success rate for rifaximin therapy in eradicating SIBO [53]. Dosages and treatment durations vary, but a common regimen involves 550 mg 3 times daily for 14 days [54]. The drug's effectiveness is attributed to its ability to reduce the bacterial load in the small intestine without significant systemic absorption, consequently minimizing adverse effects. It is often used empirically in patients with symptoms consistent with SIBO when diagnostic confirmation is not feasible, as breath tests and jejunal aspirate cultures are costly and time-consuming [51]. Given rifaximin's safety profile, it is suitable for repeated courses in the management of chronic symptoms.

There is an ongoing debate about the link between SIBO and IBS, particularly IBS-D [55]. Research shows a higher prevalence of SIBO in IBS patients (OR 3.7, 95% CI: 2.3–6.0), with IBS-D patients more likely to have SIBO than IBS-C patients [56]. However, up to 20% of healthy individuals can test positive for SIBO, making

Table 3. Overview of the published work regarding the application of rifaximin in diverticular disease

Study	Design	Participants	Intervention	Main findings	Conclusion
SUDD					
Latella et al. [43] (2003)	Multicentric open trial	968	Rifaximin 400 mg BID, 7 days/month for 1 year + fiber (Compared with fiber alone)	• Fewer symptoms (abdominal pain, bloating, tenesmus, diarrhea, abdominal tenderness) • ↓ global symptomatic score • ↓ rate of complications (diverticulitis and rectal bleeding)	Cyclic administration of rifaximin is effective in obtaining symptom relief in SUDD The incidence of episodes of acute diverticulitis is lower than that in the group with fiber alone
Colecchia et al. [44] (2007)	Multicentric RCT	307	Rifaximin 400 mg BID, 7 days/month for 2 years + fiber (compared with fiber alone)	• ↓ symptomatic score (lower abdominal pain, bloating, tenesmus, and abdominal tenderness) • ↓ complication frequency	Rifaximin plus dietary fiber supplementation is more effective in reducing symptom and complication frequency
Di Mario et al. [45] (2019)	Retrospective	816	Rifaximin 800 mg QD, 7 days/month for 8 years (compared with any other treatment on demand)	• ↓ visual analogic scale of symptoms • ↓ daily bowel movements • ↓ acute diverticulitis • ↓ disease-related mortality	Effective to relieve symptoms and reduce the risk of disease-related complications in patients with SUDD
De Bastiani et al. [40] (2021)	Retrospective observational	286	Rifaximin 400 mg BID 5, 7 or 10 days/month, up to 3 months	• ↓ visual analogic scale of symptoms	Effective for the management of SUDD
Prevention of recurrent acute diverticulitis					
Lanas et al. [46] (2012)	Multicentric RCT	165	Rifaximin 400 mg BID, 7 days/month during 1 year + fiber (compared with fiber only)	• ↓ Diverticulitis recurrence	Effective for reducing the risk of diverticulitis However, it had a relatively small sample size and a short follow-up period (only 1 year)
Tursi et al. [47] (2013)	Prospective cohort	130	Rifaximin 800 mg/day, 7 days/month (compared with mesalazine 1.6 g/day)	• Mesalazine superior in maintaining mucosal healing, reducing histological activity, and higher clinical remission	Mesalazine may be more effective than rifaximin in preventing new episodes of diverticulitis However, the non-randomized design increases the risk of selection bias and potentially confounding variables may not be adequately controlled
Festa et al. [48] (2017)	Retrospective cohort	124	Rifaximin 400 mg BID, 10 days/month (compared with mesalazine 2.4 g/day)	• Rifaximin superior with higher clinical remission and low complication rate	Rifaximin may be more effective than mesalazine in preventing new episodes of diverticulitis However, the retrospective design and lack of randomization weakens the reliability of the findings

RCT, randomized controlled trial; QD, once daily or quaque die; BID, twice daily or bis in die; TID, three times daily or ter in die; SUDD, symptomatic uncomplicated diverticular disease.

interpretation challenging [57]. So, is the rationale behind this association strong enough? A recent narrative review highlighted several important considerations [58]. While early studies using hydrogen breath tests (HBTs) suggested an association, these tests are now thought to reflect intestinal transit time and colonic bacterial activity rather than reliably diagnose SIBO [59]. Evidence indicates that SIBO is unlikely to be the primary cause of IBS, as there is no consistent temporal relationship, dose-response correlation, or uniformity in findings across studies [60]. Additionally, eliminating SIBO does not consistently resolve IBS symptoms and treatments targeting SIBO often perform worse than general IBS therapies, such as antidepressants and antispasmodics [61, 62]. Finally, confounding factors like the use of proton pump inhibitors (PPIs) – which promote SIBO and share similar side effects with IBS – further complicate the association [63]. In conclusion, while bacteria may contribute to some IBS-associated symptoms, they cannot fully explain the condition. A direct causative association between IBS and SIBO should therefore not be assumed.

Traveler's Diarrhea

Traveler's diarrhea (TD) is a common condition caused by ingestion of contaminated food or water, frequently involving enterotoxigenic *Escherichia coli*, among other pathogens [19, 64]. The condition involves an overgrowth of pathogenic bacteria in the intestines, leading to symptoms such as diarrhea, abdominal cramps, and nausea. This disruption of the normal gut microbiota exacerbates the illness and can prolong recovery time [64].

Evidence indicates that antibiotics can reduce illness duration in TD [65], though most cases are self-limiting. Due to increasing concerns about antibiotic resistance, there is growing advocacy that most cases of TD do not require antibiotic treatment and it should be reserved for moderate (defined as diarrhea that is distressing or interferes with planned activities) to severe TD (diarrhea that is incapacitating or completely prevents planned activities or even in the presence of fecal blood-dysentery) or when there is a high risk of severe illness (e.g., immunocompromised individuals) [66]. Rifaximin is an option for nondysenteric cases, which constitute the majority, given its pharmacokinetic properties, efficacy, and excellent safety profile (Table 4) [66–68]. The typical dose for treatment is 200 mg three times daily for 3 days. Research shows that rifaximin can shorten the duration of diarrhea and lessen the severity of symptoms [66].

Preventing acute gastroenteritis while traveling requires proper handwashing, eating thoroughly cooked food, drinking bottled or treated water, and avoiding ice drinks [66]. Antimicrobial prophylaxis is not routinely recommended, except for high-risk travelers (e.g., individuals with a clinically significant long-term morbidity following an enteric infection, such as reactive arthritis, or serious chronic illness that predisposes for TD-related complications). In this clinical scenario, rifaximin should be the first-line antibiotic to be considered [66]. However, there is still no consensus on the duration and dosage for this indication.

A key area of concern in IBS management is how to address the condition during travel. IBS patients often require treatments that focus on symptom relief rather than targeting an underlying immune-related disease. However, any disruption in gut function – such as an infection like TD – can significantly worsen IBS symptoms. The stress of travel, along with dietary changes and exposure to potential infections, often triggers symptom flare-ups. As a result, preventing TD in IBS patients is a complex and controversial issue, requiring a careful balance between the benefits of preventive measures, like prophylactic antibiotics, and the risks of antibiotic resistance and other complications. Consequently, prevention strategies must be tailored on a case-by-case basis.

Hepatic Encephalopathy

HE is a neuropsychiatric syndrome associated with liver dysfunction, characterized by cognitive impairment, altered mental status, and, in severe cases, coma [74]. While the pathophysiology remains complex, a prevailing theory suggests that, in cases of hepatocellular dysfunction, individuals may face a diminished capacity to metabolize toxins and nitrogenous compounds originating from the enterohepatic circulation, previously produced by gut flora [75]. Furthermore, the intestinal microbiota also plays an important role in the pathogenesis of HE through the gut-liver-brain axis [20]. In patients with liver cirrhosis, there is often an overgrowth of harmful bacteria, including ammonia-producing strains like those from the Enterobacteriaceae family, which is part of the Proteobacteria phylum [20, 21]. At the same time, there is a reduction in beneficial bacteria such as Lachnospiraceae and Ruminococcaceae, which are families within the Firmicutes phylum and play a key role in maintaining gut barrier integrity [20]. This imbalance leads to increased gut permeability and the systemic absorption of neurotoxins.

Table 4. Overview of the published work regarding the applications of rifaximin in the treatment and prevention of TD

Study	Design	Participants	Intervention	Main findings	Conclusion
Treatment of TD					
Taylor et al. [67] (2006)	Multicenter RCT	399	Rifaximin 200 mg TID, 10 days (compared with ciprofloxacin 500 mg BID and with placebo)	• Similar efficacy than quinolones to treat noninvasive agents • Lower efficacy than quinolones to treat invasive agents	Effective and safe for treating TD caused by noninvasive agents
Hong et al. [68] (2010)	Multicenter RCT	154	Rifaximin 400 mg BID, 3 days (compared with ciprofloxacin 500 mg BID, 3 days)	• Similar outcomes between the two drugs	Comparable efficacy to treat treating TD in comparison to quinolones
Prevention of TD					
Zanger et al. [69] (2013)	RCT	258	Rifaximin 200 mg every 12–18 h, for the duration of the travel (compared with placebo)	• For the entire travel and post-travel period, risk of classic TD was greater in participants in the placebo group than in those in the rifaximin group	Moderately effective in prevention of TD in individuals traveling to south and southeast Asia
Flores et al. [70] (2011)	RCT	98	Rifaximin 550 mg/day, 14 days (compared with placebo)	• Rifaximin failed to prevent TD compared with placebo, probably because of the low attack rate for illness	
Martinez-Sandoval et al. [71] (2010)	Multicenter RCT	210	Rifaximin 600 mg/day, 14 days (compared with placebo)	• Rifaximin prophylaxis reduced risk of developing TD vs. placebo	Effective and safe in preventing TD in US travelers to Mexico
Armstrong et al. [72] (2010)	RCT	100	Rifaximin 1,100 mg/day, 2 weeks (compared with placebo)	• Rifaximin provided 67% protection against TD	Effective in preventing TD among military personnel on deployment
DuPont et al. [73] (2005)	RCT	210	Rifaximin 200 mg/day OR 200 mg BID OR 200 mg TID, 2 weeks (compared with placebo)	• Rifaximin provided 72% and 77% protection against TD and antibiotic-treated TD, respectively	Effective in preventing TD in Mexico

RCT, randomized controlled trial; BID twice daily or bis in die; TID 3 times daily or ter in die.

For patients with a first episode of overt HE, secondary prophylaxis should be initiated with lactulose (titrated to obtain 2–3 bowel movements per day) and rifaximin, particularly if another episode occurs within 6 months [76]. Rifaximin is effective in preventing HE recurrence by reducing the intestinal production and absorption of ammonia and other toxins. The pivotal study by Bass et al. [74] demonstrated that rifaximin plus lactulose significantly reduced the risk of HE recurrence and HE-related hospitalizations compared to lactulose alone. The recommended dosage of rifaximin for HE is 550 mg twice daily. It is well-tolerated, with minimal adverse effects, making it a suitable long-term treatment option. The drug's safety and efficacy have led to its inclusion in clinical guidelines for the management of HE, particularly for patients with a history of recurrent episodes.

Rifaximin also shows potential in managing liver-related conditions beyond HE, such as hepatic cirrhosis and metabolic dysfunction-associated liver disease. In cirrhosis, rifaximin has shown to significantly reduce portal pressure and plasma endotoxin levels [77]. In a multicenter randomized open-label prospective trial, it was also shown that rifaximin improved transplant-free

Table 5. Overview of published work regarding the application of rifaximin in ulcerative colitis (UC), Crohn's disease (CD) and antibiotic-dependent pouchitis

Study	Design	Participants	Intervention	Main findings	Conclusion
UC					
Gionchetti et al. [95] (1999)	RCT	28 active UC refractory to corticosteroids	Rifaximin 400 mg TID, 10 days + corticosteroids (compared with placebo + corticosteroids)	• Clinical and endoscopic improvement observed, but not statistically significant	Potential benefit in UC but not statistically significant
Guslandi et al. [96] (2006)	RCT	30 mild-moderate flare up UC (steroid treatment not advisable)	Rifaximin 400 mg BID, 4 weeks + mesalazine 2.4 g ID (compared with mesalazine)	• Clinical remission and partial clinical improvement observed	Potential benefit in UC, in an add-on therapy to mesalazine
CD					
Prantera et al. [93] (2006)	RCT	83 mild-moderate active CD	Rifaximin 800 mg BID, 12 weeks (compared with placebo)	• Improvement of clinical remission observed, but not statistically significant • ↓ Treatment failures	Potential benefit in inducing remission CD, particularly reducing treatment failures
Prantera et al. [94] (2012)	Multicenter RCT	402 moderate active CD	Rifaximin EIR 400, 800, and 1,200 mg TID, 12 weeks (compared with placebo)	• Improvement of clinical remission observed, with a statistically significant difference (+rifaximin-EIR 800 mg)	Potential benefit in inducing remission CD
Pouchitis					
Shen et al. [97] (2008)	Prospective cohort	53 antibiotic-dependent pouchitis	Rifaximin 200 mg/day, 24 weeks (compared with placebo)	• Improvement of clinical remission	Effective in maintaining remission in chronic antibiotic-dependent pouchitis

RCT, randomized controlled trial; BID, twice daily or bis in die; TID, three times daily or ter in die; EIR, extended intestinal release.

survival in decompensated cases [78]. In cirrhosis-associated infections, such as spontaneous bacterial peritonitis (SBP), the potential use of rifaximin is also being explored due to the emergence of multidrug resistant organisms to the most commonly prescribed antibiotics nowadays, such as norfloxacin [79]. Elfert et al. [80] compared the efficacy of rifaximin versus norfloxacin for the secondary prevention of SBP. They found that SBP recurrence in the rifaximin group was markedly lower than in the norfloxacin group (3.88 versus 14.13% $p = 0.04$), as was the mortality rate (13.74 versus 24.43%, $p = 0.044$). Rifaximin also shows promise in other complications of liver disease, such as refractory ascites. Hanafy et al. [81] explored the efficacy of combined therapy with rifaximin and midrodrine in this context. Indeed, rifaximin plus midodrine improved circulatory and renal function, prolonging patient survival [81]. Another potential application is secondary prophylaxis of variceal hemorrhage. Zubieta-Rodeíguez et al. [82] conducted an observational cohort study on a tertiary care center and concluded that patients who continue rifaximin therapy after discharge have a reduced risk of variceal bleeding and HE recurrence. In metabolic dysfunction-associated liver disease, rifaximin appears to reduce inflammation, endotoxins, and metabolic markers, but evidence regarding its long-term efficacy remains inconclusive [83]. Despite these promising findings, further research is needed to establish its broader role in liver disease management.

Table 6. Summary table with the therapeutic indications for rifaximin and regimens by indication

Disorder	Recommended regimen
IBS with diarrhea	550 mg TID (14 days)
Diverticular disease	
Symptomatic uncomplicated diverticular disease	400 mg BID (7–10 days/month for 12–24 months)
Symptom relief	
Primary and secondary prevention of acute diverticulitis	
SIBO	550 mg TID (14 days)
TD	
Treatment	200 mg TID (3 days)
Prevention	Nonconsensual, but we recommend 200 mg BID (for the duration of the travel)
HE	550 mg BID (chronically)
Recurrent CDI	400 mg TID (20 days, after standard antibiotic treatment)
IBD	
Pouchitis	2 g QID (4 weeks)

Clostridioides difficile Infection

Clostridioides difficile is a gram-positive, anaerobic, spore-forming, toxin-producing bacillus that can cause CDI, a healthcare-associated concern that ranges from mild diarrhea to life-threatening colitis [84]. CDI typically follows a disruption of the normal gut microbiota, often due to broad-spectrum antibiotic use. This disruption results in a loss of colonization resistance, allowing the overgrowth of *C. difficile* [84]. The dysbiosis in CDI is characterized by a decrease in beneficial bacteria such as Firmicutes and Actinobacteria and an increase in Proteobacteria, including pathogenic species [22, 23].

The treatment of an initial episode of CDI typically involves antibiotic therapy with fidaxomicin, vancomycin, or metronidazole. Rifaximin has shown effectiveness, particularly in the treatment of recurrent CDI cases [85]. The drug's use is based on its ability to target *C. difficile* while sparing other beneficial gut bacteria, thus maintaining a more balanced gut microbiome. The 2011 pilot study by Garey et al. [86] demonstrated a significant reduction in recurrent diarrhea among patients treated with rifaximin following standard CDI treatment. Although the difference in CDI recurrence was not statistically significant, the study suggested a potential role for rifaximin in managing recurrent cases. To the best of our knowledge, only one study has examined the use of rifaximin as the first line in CDI. However, this study was conducted in a highly specific population – pediatric patients with IBD – finding no significant differences in cure or recurrence rates compared to metronidazole [87]. Therefore, there is not enough evidence to support rifaximin's use as a first-line treatment for CDI.

Rifaximin has shown promise in preventing recurrent CDI. In 2019, a RCT evaluated whether treatment with rifaximin following the resolution of CDI with standard therapy (vancomycin or metronidazole) would reduce recurrence, when compared to placebo. The dosage was tapered from 400 mg 3 times daily for 14 days to 200 mg 3 times daily for an additional 14 days. Recurrence within 12 weeks was 29.5% in the placebo group and 15.9% in the rifaximin group, a difference of 13.7% (95% CI: −28.1% to 0.7%, $p = 0.06$). It was concluded that rifaximin may reduce the risk of recurrence, but the confidence interval does not rule out the possibility of no effect [88].

In conclusion, rifaximin has shown promise in treating and preventing recurrent infections. However, various guidelines addressing this topic provide contradictory recommendations. On one hand, the ACG clinical guidelines acknowledge its efficacy yet recommend against its routine use [89]. On the other hand, the IDSA and ESCMID guidelines advocate for its use as an "add-on" therapy in patients with multiple recurrences following standard-of-care antibiotics [85, 90].

Inflammatory Bowel Disease

IBD, comprising Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic inflammation of the GI tract. The microbiota plays a key

role in IBD pathogenesis. CD is associated with genetic polymorphisms affecting the innate immune response and Paneth cell function, which are crucial for microbial defense [91]. These genetic factors may contribute to chronic inflammation by triggering immune responses in susceptible individuals [91]. Indeed, in CD, there is an increase in the prevalence of *Campylobacter concisus* and *E. coli*, and a decrease in commensal, anti-inflammatory bacteria such as *Faecalibacterium prausnitzii*. In UC, it is has been suggested that *Fusobacterium varium* can promote the development of this pathology [24]. Additionally, it is well known that these patients often suffer concomitantly from IBS, another condition based on gut dysbiosis [92].

Despite the potential role of dysbiosis in the pathogenesis of IBD, attempts to manipulate the intestinal microbiome in IBD have yielded mixed results (Table 5). For instance, Prantera et al. [93] reported a 52% remission rate in CD patients treated with rifaximin, though the results were not statistically significant. A subsequent trial with an extended-release formulation showed a statistically significant remission rate of 62% [94]. Regarding UC, there are currently few studies concerning the use of rifaximin, the most robust of which are listed in Table 5.

Pouchitis, a complication affecting up to 50% of patients within 10 years after ileal pouch-anal anastomosis for UC, is characterized by inflammation of the ileal pouch. Symptoms include increased bowel movements, abdominal pain, and urgency [97]. These patients often develop an antibiotic-dependent form of pouchitis, requiring long-term antibiotic therapy to maintain remission. Typically, if symptoms persist for more than 4 weeks, the condition is considered chronic pouchitis. Rifaximin has been effective in managing chronic antibiotic-dependent pouchitis [98]. An open-label cohort study by Shen et al. [97] demonstrated that rifaximin maintained remission in 65% of patients at 3 months, with continued efficacy at 6 and 12 months. In fact, the ECCO guidelines recommend rifaximin as an alternative treatment for chronic pouchitis at a dose of 2 g daily for 4 weeks, highlighting its role in maintaining remission and managing symptoms [99].

Despite some positive findings, rifaximin is not widely recommended for IBD management outside of specific contexts, like antibiotic-dependent pouchitis. More research is needed to determine the drug's efficacy and identify patient subgroups that may benefit from its use. Current guidelines do not advocate routine use of antibiotics for uncomplicated CD or UC due to a lack of consistent evidence.

In summary, the applicability of rifaximin extends to various GI conditions. Table 6 shows a summary outlining the proposed therapeutic regimens of rifaximin for each indication.

Conclusion

Dysbiosis plays a key role in the pathophysiology role of various diseases, often linked to disruptions in the gut-brain axis and a pro-inflammatory state. Rifaximin is a valuable therapeutic option due to its modulatory effects, especially considering its minimal side effects. Given the high prevalence of conditions like IBS, SIBO, HE, TD, and IBD, it is crucial for gastroenterologists to be well-versed with when, how and for whom this treatment should be utilized. In other cases, such as diverticular disease and CDI, although the use of rifaximin remains controversial, there may still be a therapeutic rationale for its application.

Statement of Ethics

All papers must contain the following statements after the main body of the text and before the reference list. More detailed information can be found at Publication Ethics and Editorial Policies|Karger Publishers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: Armando Peixoto; resources: Armando Peixoto, Joana Frias, and Miguel Martins.; writing – original draft preparation: Joana Frias and Miguel Martins (equally contribution); writing – review and editing, Joana Frias, Miguel Martins, Armando Peixoto, and Guilherme Macedo.; supervision and project administration: Armando Peixoto and Guilherme Macedo. All authors have read and agreed to the published version of the manuscript.

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