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REVIEW

Effect of rifaximin on gut microbiota composition in advanced liver disease and its complications

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Abstract

Liver cirrhosis is a paradigm of intestinal dysbiosis. The qualitative and quantitative derangement of intestinal microbial community reported in cirrhotic patients seems to be strictly related with the impairment of liver function. A kind of gut microbial "fingerprint", characterized by the reduced ratio of "good" to "potentially pathogenic" bacteria has recently been outlined, and is associated with the increase in Model for End-Stage Liver Disease and Child Pugh scores. Moreover, in patients presenting with cirrhosis complications such as spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), and, portal hypertension intestinal microbiota modifications or the isolation of bacteria deriving from the gut are commonly reported. Rifaximin is a non-absorbable antibiotic used in the management of several gastrointestinal diseases. Beyond bactericidal/bacteriostatic, immune-modulating and anti-inflammatory activity, a little is known about its interaction with gut microbial environment. Rifaximin has been demonstrated to exert beneficial effects on cognitive function in patients with HE, and also to prevent the development of SBP, to reduce endotoxemia and to improve hemodynamics in cirrhotics. These results are linked to a shift in gut microbes functionality, triggering the production of favorable metabolites. The low incidence of drug-related adverse events due to the small amount of circulating drug makes rifaximin a relatively safe antibiotic for the modulation of gut microbiota in advanced liver disease.

Key words: Liver cirrhosis; Gut microbiota; Rifaximin; Hepatic encephalopathy; Spontaneous bacterial peritonitis; Ascites; Endotoxemia; Thrombocytopenia

Core tip: Advanced liver disease is characterized by intestinal dysbiosis, which has been involved in the pathogenesis of complications. Rifaximin is able to improve cognitive tests and practical abilities, to reduce

the risk of hepatic encephalopathy (HE) recurrence and the number of HE-related hospitalizations. Rifaximin efficacy seems not associated with major changes in gut bacteria composition but rather with a shift in the microbiome functionality. Rifaximin is useful in the prevention of spontaneous bacterial peritonitis in patients with ascites. Rifaximin reduces endotoxemia and has beneficial effects on cirrhotic patients hemodynamics, reducing the incidence of complications related to portal hypertension.

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INTRODUCTION

Rifaximin is a non-systemic antibiotic approved for the treatment of traveler's diarrhea, irritable bowel syndrome (IBS) with diarrhea and overt hepatic encephalopathy (HE)[1]. It has *in vitro* bactericidal and bacteriostatic activity against aerobic and anaerobic Gram-positive and Gram-negative species, being also able to reduce bacterial virulence and translocation, and to inhibit bacterial adherence to gut mucosa[2-7].

Due to the low systemic absorption (only 0.4% of the oral administered dose), rifaximin has an optimal tolerability profile, and side effects as well as the induction of bacterial resistance are nearly lacking[1,8,9].

Beyond that, rifaximin has particular features which are not typical of a common antibiotic molecule. *In vitro* and *in vivo* models and preliminary experiences in humans[10-14] have demonstrated that rifaximin does not change the overall composition of the gut microbiota while it is able to provide minimal changes, such as promoting the growth of bacteria beneficial to the gut. Nevertheless, rifaximin modulates the release of inflammatory cytokines[15,16] and increases NF-κB expression, exerting anti-inflammatory effects that could counteract the pro-inflammatory response observed in conditions of gut microbiota derangement[17].

Based on these evidences, rifaximin use has been extended to the management of pathologies associated with gut microbiota deregulation such as irritable bowel syndrome[11,18-21], inflammatory bowel diseases[10,13,22-30], diverticular disease[31-36] and liver cirrhosis and its complications.

Liver cirrhosis is a paradigm of intestinal dysbiosis. Indeed, the physiological partitioning of the gastrointestinal tract is deranged in cirrhotic patients, due to the decreased secretion of gastric acid (often favored by medications[37]), to the reduced gastrointestinal motility, to the impaired systemic and mucosal immune response and to the low concentration of bile acids in the colon[38]. The epiphenomenon of this chronic dysfunction is a profound alteration of the gut microbiota composition, which is both quantitative (Small Intestinal Bacterial Overgrowth, SIBO) and more pronounced in the advanced stages of the disease and in case of decompensation (Figure 1).

This is the rationale for gut microbiota modulation in patients with liver cirrhosis, especially in those with severe impairment of liver function presenting with complications.

THE "FINGERPRINT" OF GUT MICROBIOTA IN LIVER CIRRHOSIS

The introduction of metagenomic techniques such as 16S rRNA-based pyrosequencing has recently allowed to identify which modifications of the gut microenvironment are the most frequently observed in liver cirrhotic patients[39]. The human gut hosts a bacterial core community involved in maintaining gastrointestinal health and mainly composed of the phyla Bacteroidetes and Firmicutes, which include the genera *Bacteroides*, *Clostridium clusters XIVa* and *IVa*, *Eubacterium*, *Faecalibacterium*, *Lactobacillus*, and *Roseburia*. In patients affected by liver cirrhosis, at the phylum level, Bacteroidetes are decreased in favor of Fusobacteria and Proteobacteria, such as Enterobacteriaceae and Pasteurellaceae[40-42]. Looking at family, genus and species division, the increase in Enterobacteriaceae, Streptococcaceae and Veillonellaceae abundance has been reported in cirrhotic patients compared with healthy controls, whereas Lachnospiraceae, Ruminococcaceae, *Clostridium clusters XI* and *XIVab*, lactic acid bacteria, Bifidobacteria and *Faecalibacterium prausnitzii* seem to be reduced[40-46]. Notably, Enterobacteriaceae family includes *Escherichia coli* and *Klebsiella spp.*, key bacteria in the pathogenesis of spontaneous bacterial peritonitis (SBP). In addition to the unbalance between potentially pathogenic and beneficial bacteria, the major part of the metagenomic species enriched in cirrhotics' fecal samples belong to *Veillonella* or *Streptococcus* taxa, which usually derive from the mouth or the small intestine[47]. Although this may apparently confirm the subversion of the gastrointestinal physiology occurring during the course of liver disease, when cirrhotics' salivary microbiota is specifically analyzed and compared with the fecal one, they seem significantly different rather than similar[46]. More in detail, Streptococcaceae are prevalent in the saliva, whereas stools are characterized by a reduction in the autochthonous taxa Lachnospiraceae, Ruminococcaceae, and Clostridiales XIV. However, about half of samples analyzed in this study belonged to patients who have had previous episodes of HE and were on lactulose, with the addition of rifaximin in

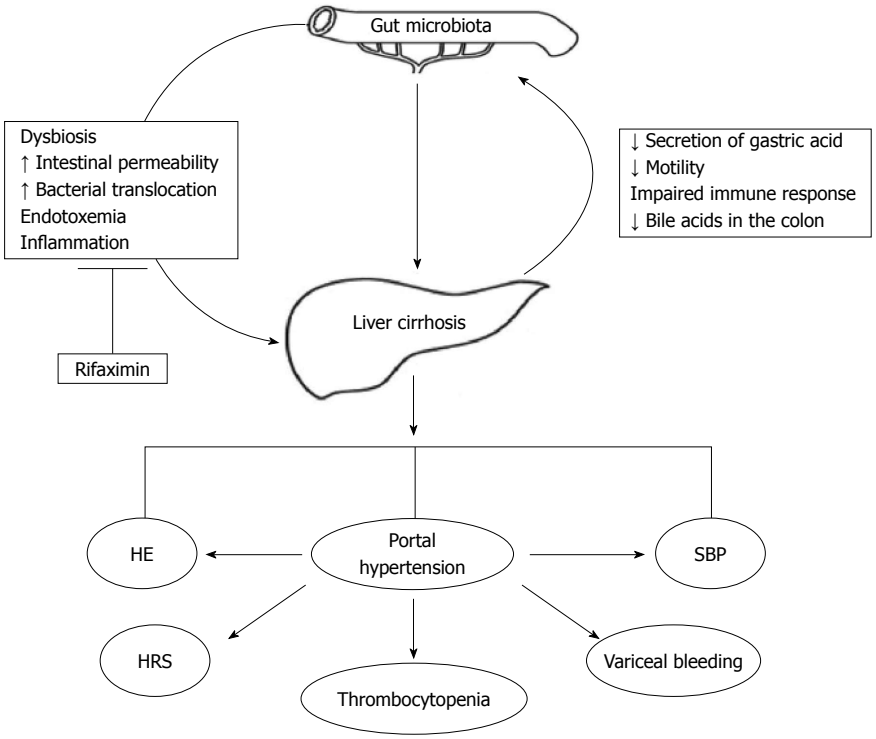

Figure 1 Effects of Rifaximin on gut-liver axis. Rifaximin decreases endotoxemia and inflammation both directly and indirectly, by reducing bacterial translocation, counteracting bacterial overgrowth and modulating gut microbiota composition and function. Due to these peculiar effects, rifaximin is used for the treatment of advanced liver disease complications. HE: Hepatic encephalopathy; SIBO: Small intestinal bacterial overgrowth; SBP: Spontaneous bacterial peritonitis; HRS: Hepatorenal syndrome.

two cases. Further analyses to discriminate conditions predisposing to the "mixing-up" of bacteria from different sites of the gastrointestinal tract are needed to quell this debate.

Interestingly, the alteration of gut microbiota composition seems to have a prognostic significance, or at least to follow the evolution of liver disease. Generally speaking, Qin *et al*[47] demonstrated that metagenomic species enriched in cirrhotic patients correlate with the severity of the disease, in a proportion dependent on bacterial load. In other studies, the reduction in Clostridiaceae as well as in Veillonellaceae and in Porphyromonadaceae has been associated with inflammation and with the progression of liver disease and Streptococcaceae have been reported to correlate positively with Child Pugh score in contrast to Lachnospiraceae which correlated negatively[41,43,48].

Taking together these findings, cirrhotic patients' microbiota is characterized by a higher proportion of potentially pathogenic bacteria, lacking of those species recognized as beneficial to intestinal health and homeostasis. Notwithstanding, the reduction in the ratio between "good" (*e.g.*, Lachnospiraceae, Ruminococcaceae and Clostridia cluster XIV) and potentially "bad" bacteria (*e.g.*, Staphylococcaeae, Enterobacteriaeceae and Enterococcaceae) - namely "cirrhosis dysbiosis ratio" or CDR - is characteristic of the individuals with a more severe disease, such as cirrhotic outpatients and inpatients[48].

Given the evidence that the progression of liver disease is associated with a change in the gut microenvironment, liver cirrhosis complications consequently grow in the soil of intestinal dysbiosis.

RIFAXIMIN AND GUT MICROBIOTA MODULATION IN ADVANCED LIVER DISEASE AND ITS COMPLICATIONS

Rifaximin and gut microbiota modulation in HE

Several differences have been reported in the gut microbiota of cirrhotic patients with or without HE. In patients with minimal HE, Streptococcaceae represent the prevalent bacterial family, and the abundance of *Streptococcus salivarius*, which is involved the production of ammonia, is increased[45]. Alcaligeneceae, Porphyromonadaceae and Enterobacteriaceae have also been associated with HE in cirrhotics; in particular, Alcaligeneceae and Porphyromonadaceae are significantly linked with poor cognitive performance, and Enterobacteriaceae with a worse MELD score[49]. In addition, a decreased CDR has been reported in cirrhotic patients with HE[48]. Similar results have been obtained by the analysis of mucosal microbiome from sigmoid biopsies: *Enterococcus*, *Veillonella*, *Megasphaera*, *Bifidobacterium*, and *Burkholderia* were predominant in patients with HE, whereas cirrhotics without HE presented an increased abundance of the "good" genus *Roseburia*, and the healthy controls

an increased abundance of *Dorea*, *Subdoligranulum*, *Incertae Sedis XIV*, *Blautia*, *Roseburia*, *Faecalibacterium* and a few pathogenic genera[50]. Since the intestinal microenvironment of cirrhotics without HE has been demonstrated to be closer to healthy people's one[46], it is not surprising that, in patients with HE, the more the mucosal microbiota resembled that of controls, the better was the cognitive performance and the lower were the serum markers of inflammation[50].

Studies focused on clinical outcomes reported a high efficacy of rifaximin in cirrhotics with HE and a mild/moderate stage of disease. A randomized, double-blind, placebo-controlled trial including 299 patients has proved that rifaximin with or without lactulose is able to reduce the risk of HE recurrence and the rate of HE-related hospitalization, especially in patients with MELD score < 18[51]. Similar results were also obtained in other studies including patients in different stages of liver disease, receiving various treatment schedules (Table 1)[52-58].

In addition to the roughly evident benefits on overt HE, rifaximin has also been reported to improve operational abilities and input integration capacity in patients with minimal HE, as demonstrated by the amelioration of driving simulator performance[59]. This positive shift in cognitive tests and practical abilities is undoubtedly accompanied by a significant improvement in health-related quality of life[60,61].

At the microscopic level, rifaximin does not seem to change stool microbiota composition in patients with minimal HE, and only a reduction in Veillonellaceae and an increase in Eubacteraceae have been observed[62]. Reasonably, the improvement in cognitive function and the reduced endotoxemia associated with rifaximin treatment derive from a beneficial modulation of gut microbiota metabolic profile rather than from a major rearrangement of the intestinal microbial community. Indeed, the Authors reported an increase in saturated and unsaturated fatty acids and in serum fructose, succinic acid and citramalic acid production after rifaximin treatment, but the most relevant finding was the modification of correlation networks involving several bacteria (Enterobacteriaceae, Bacteroidaceae, Veillonellaceae, Porphyromonadaceae and Rikenellaceae), metabolites and clinical outcomes, suggesting a functional change in the gut microbiome. Although only patients with minimal HE have been included and some selection biases could be identified, the study by Bajaj *et al*[62] is to date the only published experience reporting the metagenomic and metabolomic changes produced by rifaximin treatment in cirrhotics with minimal HE. Nevertheless, despite the good results in terms of efficacy, rifaximin role in the treatment of cirrhotics at high risk of developing HE, such as patients with high MELD scores or with transjugular intrahepatic portosystemic shunts or surgical portosystemic shunts or those with a recent episode of acute variceal bleeding, needs to be further investigated[63-65].

Rifaximin and gut microbiota modulation in SBP

Ascites and SBP are typical manifestations of decompensated liver disease. SIBO and bacterial translocation are the mainstay of SBP. Indeed, SIBO prevalence among cirrhotics is high, ranging between 30% and 70%[38] and it has been associated with the development of SBP due to the translocation of intestinal bacteria to the systemic circulation and the ascitic fluid[66]. Gram-negative bacteria such as *Escherichia coli* and *Klebsiella spp.* as well as Pneumococci, Streptococci and other Gram-positive and Gram-negative bacteria have been identified in 50% of cases by culture-based analysis of ascitic fluid[67]. However, bacterial DNA can be recognized in the ascites of half of cirrhotics even in absence of SBP and with negative cultures[44], and several studies identified microbes usually present within the gut[41,43,68]. Ascites microbial composition is linked with the stage of liver disease; indeed, Child-Pugh score is correlated with ascitic bacteria similarity and ascitic neutrophil count, further strengthening the connection between gut microbiota and liver cirrhosis progression[68].

Therefore, it has been hypothesized that rifaximin, being effective on SIBO, could be useful in preventing SBP. In the retrospective study by Hanouneh *et al*[66] a 72% reduction in SBP occurrence and a transplant free survival of 72% were observed in the 49 cirrhotic patients with ascites who received rifaximin (Table 2).

Another prospective observational study reported that different bacterial species could be identified in the ascitic fluid of patients receiving rifaximin compared to those who did not receive SBP prophylaxis[69]. Indeed, Enterococci and *Escherichia coli* were isolated from the ascites of patients without prophylaxis and *Klebsiella spp.* were isolated in those on rifaximin. However, this finding had no predictive value, since the incidence of SBP was similar between the two groups.

Rifaximin, gut microbiota modulation and liver hemodynamics

Intestinal decontamination improves hemodynamics in animal models of cirrhosis by reducing endotoxemia related to bacterial translocation[70]. Similar results have also been obtained in humans[71], and have been associated with a lower incidence of complications (Table 3).

Twenty-three patients with decompensated alcoholic cirrhosis who achieved a reduction of hepatic venous pressure gradient (HVPG) after 28 d of rifaximin treatment were then followed-up for 5 years[72]. Compared to matched controls, rifaximin group showed a lower incidence of complications related to portal hypertension, such as variceal bleeding, HE, SBP and hepatorenal syndrome, and a better survival compared to controls. Other studies confirmed a reduction in

Table 1 Major studies describing the changes in gut microbiota composition and the effects of rifaximin treatment in patients with advanced liver disease and hepatic encephalopathy

Study	Study design	No. patients	Disease severity	HE type	Treatment schedule	Results	Safety
Mas *et al*[56] 2003	Prospective randomized, double-blind, double-dummy, controlled trial	103	Not reported	Overt HE	50 pts rifaximin 1200 mg/d for 5-10 d 53 pts lactitol 60 g/d for 5-10 d	Improved neuropsychiatric and psychometric parameters in both groups Reduced blood ammonia levels in both groups No significant differences in efficacy (resolution/improvement 81.6% rifaximin *vs* 80.4% lactitol; unchanged/failure 18.4% rifaximin *vs* 19.6% lactitol) HE complete resolution: 53.1% rifaximin *vs* 37.2% lactitol	Abdominal pain: 4% rifaximin Mild diarrhea: 2% lactitol Vomiting: 2% lactitol
Paik *et al*[57] 2005	Prospective randomized		CTP: rifaximin A: 0%, B: 50%, C: 50% lactulose A: 0%, B: 64%, C: 36%	Overt HE	32 pts rifaximin 400 mg TID for 7 d 22 pts lactulose 90 mL/d for 7 d	Reduction in blood ammonia levels similar in both groups Improvement in HE grade and index similar in both groups Improvement in HE grade similar in both groups	Abdominal pain: 3% rifaximin Severe diarrhea: 4.5% lactulose
Leevy *et al*[58] 2007	Retrospective	145	Not reported	Overt HE	Lactulose 30 cc BID for ≥ 6 mo followed by rifaximin 400 mg TID for ≥ 6 mo	HE grade Ⅲ or Ⅳ: 6% after rifaximin 25% after lactulose ($P < 0.001$) Asterixis: 63% after rifaximin *vs* 93% after lactulose ($P < 0.001$)	Hospitalizations (mean number): 0.5 rifaximin period *vs* 1.6 lactulose period ($P = 0.001$) Hospitalizations days (mean): 2.5 rifaximin period *vs* 7.3 lactulose period ($P = 0.001$) Diarrhea: 89% during lactulose, 99% during rifaximin Flatulence: 100% during lactulose, 100% during rifaximin Abdominal pain: 100% during lactulose, 100% during rifaximin Headache: 100% during lactulose, 99% during rifaximin However, severe adverse events were more common in the lactulose period ($P < 0.001$)
Bass *et al*[51] 2010	Prospective, randomized, double-blind, placebo-controlled	299	MELD score (%): rifaximin ≤ 10: 24.3% 11-18: 67.1% 19-24: 8.6% placebo: ≤ 10: 30.2% 11-18: 60.4% 19-24: 8.8%	Overt HE	140 pts 550 mg BID for 6 mo 159 pts placebo 90% of pts also received lactulose	Rifaximin is more effective than placebo in maintaining HE remission ($P < 0.001$) Breakthrough episodes rate: 22.1% rifaximin *vs* 45.9% placebo Risk of HE-related hospitalization: 13.6% rifaximin *vs* 22.6% placebo ($P = 0.01$)	Incidence of adverse events was similar in the two groups; most frequently reported: nausea diarrhea, fatigue Bacterial peritonitis: 1.4% rifaximin *vs* 2.5% placebo Bacteremia: 0.7% rifaximin *vs* 1.3% placebo *C. difficile* infection: 1.4% rifaximin *vs* 0% placebo Sepsis: 0% rifaximin *vs* 1.3% placebo

Bajaj *et al*[59] 2011	Prospective, randomized, double-blind, placebo-controlled	42	MELD score (mean) rifaximin: 9 placebo: 9	Minimal HE	21 pts rifaximin 550 mg BID 21 pts placebo for 8-wk	Total driving errors improvement: 76% rifaximin *vs* 31% placebo (P = 0.013), with a significant reduction of speeding tickets (P = 0.005) and illegal turns on navigation (P = 0.01) Cognitive performance improvement: 91% rifaximin *vs* 61% placebo (P = 0.01) Improved psycho-social dimension (quality of life assessment by Sickness Impact Profile questionnaire) in the rifaximin group compared with the placebo group (P = 0.04)	Infections rate: 0% Hospitalization rate: 0% Nausea: 14% rifaximin *vs* 14% placebo Self-limited vomiting: 5% rifaximin *vs* 5% placebo Abdominal pain: 24% rifaximin *vs* 24% placebo Flatulence: 19% rifaximin *vs* 43% placebo Headache: 19% rifaximin *vs* 33% placebo Flu-like symptoms: 5% rifaximin Constipation: 5% rifaximin Self-limited diarrhea: 5% rifaximin *vs* 5% placebo Hitching: 5% placebo Anorexia and dry mouth: 5% placebo
Neff *et al*[52] 2012	Retrospective	203	MELD score (mean, range): rifaximin 12 (8-27) rifaximin + lactulose 13 (11-26)	Overt HE	149 pts rifaximin monotherapy (400-1600 mg/d) 54 pts rifaximin (600-1200 mg/d) + lactulose (90 mL/d) dual therapy	1-yr HE remission rate: 81% rifaximin *vs* 67% rifaximin + lactulose Lower incidence of overt HE episodes in pts with mean MELD score ⩽ 20	Incidence of gastrointestinal bleeding, infection, hospitalization for dehydration/overt HE similar in both groups
Bajaj *et al*[62] 2013	Prospective	20	MELD score (mean ± SD): 9.8 ± 3.3	Minimal HE	550 mg BID for 8 wk	Significant improvement in cognitive performance on all tests apart from the block design test Significant improvement in serum bilirubin but not the other MELD score components No significant microbial change (modest reduction in Veillonellaceae and increase in Eubacteriaceae) Significant increase in serum saturated (myristic, caprylic, palmitic, palmitoleic, oleic and eicosanoic) and unsaturated (linoleic, linolenic, gamma-linolenic and arachnidonic) fatty acids, serum fructose, succinic acid and citramalic acid Change in correlation networks involving several bacteria (Enterobacteriaceae, Bacteroidaceae, Veillonellaceae, Porphyromonadaceae and Rikenellaceae) reflecting a functional shift in the gut microbiome	Not reported
Sharma *et al*[53] 2013	Prospective, randomized, double-blind, placebo-controlled	120	CTP score (mean ± SD): group A 9.9 ± 2.8 group B 9.4 ± 2.5 MELD score (mean ± SD): group A 24.9 ± 6.6 group B 23.8 ± 5.18	Overt HE	group A (63 pts): lactulose + rifaximin 1200 mg/d group B (57 pts): lactulose + placebo	HE remission rate: 76% group A *vs* 50.8% group B (P < 0.004) Mortality: 23.8% group A *vs* 49.1% group B (P < 0.05). Death was mainly due to sepsis Hospital stay (mean ± SD): 5.8 ± 3.4 in group A *vs* 8.2 ± 4.6 group B (P = 0.001)	Diarrhea: 13% group A *vs* 10% group B (P > 0.05) Abdominal pain: 6% group A *vs* 7% group B (P > 0.05)

Maharshi *et al*[54] 2014	Prospective, randomized, controlled	120 pts with acute variceal bleeding and no HE	CTP and MELD scores comparable between groups but not reported	Overt HE	60 pts lactulose 30 mL QID 60 pts rifaximin 400 mg TID for 5 d	Incidence of HE: 15% rifaximin *vs* 17% lactulose ($P = 1$) Mortality: 17% rifaximin *vs* 13% lactulose ($P = 1$) Hospital stay (mean ± SD): 10.6 ± 3.1 d rifaximin *vs* 12.4 ± 3.5 lactulose (pts with HE, $P = 0.35$); 6.3 ± 1.6 rifaximin *vs* 6.9 ± 1.9 lactulose (pts without HE, $P = 0.18$)	Rifaximn group: 5% abdominal pain and nausea Lactulose group: 26.6% diarrhea, 15% abdominal bloating
Sharma *et al*[55] 2014	Prospective, randomized, controlled	124	CTP LOLA A: 22.5%, B: 42%, C: 35.5% rifaximn A: 39%, B: 32%, C: 29% probiotics A: 19%, B: 66%, C: 16% placebo A: 33%, B: 27%, C: 40%	Minimal HE	31 pts LOLA 3 g TID for 2 mo 31 pts rifaximin 400 mg TID for 2 mo 32 pts probiotics BID for 2 mo 30 pts placebo	LOLA, rifaximin, and probiotics are superior to placebo in improving critical flicker frequency score LOLA, rifaximin, and probiotics are superior to placebo in improving neuropsychometric tests	Not reported

MELD: Model for end stage liver disease; HE: Hepatic encephalopathy; CTP: Child turcotte pugh; LOLA: L-ornithine L-aspartate.

Table 2 Major studies describing the efficacy of rifaximin in preventing episodes of spontaneous bacterial peritonitis in patients with advanced liver disease

Study	Study design	No. patients	Disease severity	Disease complication	Treatment schedule	Results	Safety
Hanouneh *et al*[66] 2012	Retrospective	404	MELD score (mean ± SD): rifaximin: 17.6 ± 7.7 no rifaximin 17.7 ± 7.5 CTP score rifaximin B: 6.1%, C: 93.9% no rifaximin B: 33%, C: 67%	SBP	49 pts received rifaximin 400 mg TID mainly for HE (recurrent HE or intolerance to lactulose)	SBP incidence: 11% in pts on rifaximin *vs* 32% in controls ($P = 0.002$) 72% SBP reduction rate in rifaximin group after adjusting for MELD score, CTP score, serum sodium, and ascitic fluid total proteins ($P = 0.007$) 72% transplant-free survival for pts on rifaximin *vs* 57% for controls ($P = 0.045$)	Not reported
Lutz *et al*[69] 2014	Prospective, observational	152	CTP score: no prophylaxis: A: 1%, B: 57%, C: 43% rifaximin: A: 0%, B: 33%, C: 67% systemically absorbed antibiotics: A:12%, B: 47%, C: 41%	SBP	Group 1 (108 pts): no prophylaxis Group 2 (27 pts): rifaximin 400 mg TID Group 3 (17 pts): systemically absorbed antibiotic prophylaxis	SBP occurrence rate: 32/152 (21%) overall, 22.2% group 1, 29.6% group 2 and 0% group 3 ($P = 0.02$ group 2 *vs* group 3 and $P = 0.04$ group 1 *vs* group 3)	Data available for SBP pts only Nosocomial infections: 38% rifaximin *vs* 54% no rifaximin ($P = 0.690$) Isolation of bacteria resistant to Ⅲ generation cephalosporin: 25% rifaximin *vs* 46% no rifaximin Isolation of multidrug resistant bacteria: 25% rifaximin *vs* 9% no rifaximin

SBP: Spontaneous bacterial peritonitis; CTP: Child turcotte pugh.

Table 3 Available studies describing the effects of rifaximin on endotoxemia in patients with advanced liver disease

Study	Study design	No. patients	Disease severity	Treatment schedule	Results	Safety
Vlachogiannakos *et al*[71] 2009	Prospective	30	welve patients (40%) were Child-Pugh B and 18 (60%) Child-Pugh C CTP score: A: 0%, B: 40%, C: 60% MELD score (mean, range): 17 (11-27) B: 40%, C: 60%	Rifaximin 1200 mg/d for 28 d	Median (range) plasma endotoxin levels decreased significantly after rifaximin administration both in systemic [1.45 (0-3.1) *vs* 0.7 (0-2.7), $P < 0.0001$] and splanchnic circulation [1.8 (0-3.4) *vs* 0.8 (0-2.1), $P < 0.0001$]. Meanwhile, the difference seen in endotoxin levels between the splanchnic and systemic circulation at day 0 ($P = 0.001$) was not noted at day 29 ($P = 0.137$) Reduction in endotoxin levels in both systemic and splanchnic circulation compared to baseline ($P < 0.0001$) Reduction in HVPG compared to baseline ($P < 0.0001$) Reduction in HVPG correlated with hepatic vein endotoxin values ($P = 0.023$)	Abdominal pain: 3% Self-limited diarrhea: 3%
Kalambokis *et al*[73] 2012	Prospective	9	CTP score: B: 56%, C: 44%	8-wk course of rifaximin (1200 mg/d) Rifaximin 1200 mg/d for 8 wk	Rifaximin significantly reduced plasma endotoxin levels Reduction in plasma endotoxin levels compared to baseline ($P < 0.01$)	Not reported
Vlachogiannakos *et al*[72] 2012	Prospective	69	welve patients (40%) were Child-Pugh B and 18 (60%) Child-Pugh C CTP score rifaximin A: 0%, B: 48%, C: 52% controls: A: 0%, B: 48%, C: 52% MELD score (mean ± SD) rifaximin: 17.2 ± 3.6 controls: 16.6 ± 3.5	23 pts who achieved a decrease in HVPG after 28-d rifaximin treatment[71] 46 cirrhotic controls	Median (range) plasma endotoxin levels decreased significantly after rifaximin administration both in systemic [1.45 (0-3.1) *vs* 0.7 (0-2.7), $P < 0.0001$] and splanchnic circulation [1.8 (0-3.4) *vs* 0.8 (0-2.1), $P < 0.0001$]. Meanwhile, the difference seen in endotoxin levels between the splanchnic and systemic circulation at day 0 ($P = 0.001$) was not noted at day 29 ($P = 0.137$) Reduction in plasma endotoxin levels in both systemic and splanchnic circulation compared to baseline ($P < 0.0001$) Risk of developing variceal bleeding: 35% rifaximin *vs* 59.5% controls ($P = 0.011$) Incidence of HE: 31.5% rifaximin *vs* 47% controls ($P = 0.034$) Incidence of SBP: 4.5% rifaximin *vs* 46% controls ($P = 0.027$) Incidence of HRS: 4.5% rifaximin *vs* 51% controls ($P = 0.037$)	Nausea: 9% Self-limited rash in the extremities: 4% Persistent diarrhea: 4%
Kalambokis *et al*[75] 2012	Prospective, randomized, placebo-controlled	23	CTP score rifaximin: A: 0%, B: 46%, C: 54% placebo: A: 0%, B: 40%, C: 60%	13 pts: rifaximin 1200 mg/d for 4 wk 10 cirrhotic pts: placebo	Reduction in endotoxin levels compared to control group ($P = 0.005$) Increase in mean platelets count in rifaximin group compared to controls ($P = 0.006$)	Not reported
Bajaj *et al*[62] 2013	Prospective	20	MELD score (mean ± SD): 9.8 ± 3.3	Rifaximin 550 mg BID for 8 wk	Reduction in plasma endotoxin levels compared to baseline ($P = 0.02$)	Not reported

MELD: Model for end stage liver disease; CTP: Child turcotte pugh; HVPG: Hepatic venous pressure gradient.

endotoxemia, serum bilirubin, Child-Pugh and MELD scores, together with an increase in serum albumin levels after rifaximin treatment[62,73].

Rifaximin has also been demonstrated to have beneficial effects in the treatment of thrombocytopenia, the pathogenesis of which has not been completely clarified yet in cirrhotics. Endotoxemia has been advocated to contribute, together with portal hypertension, in the development of thrombocytopenia in these patients[74]; indeed, a small prelimiary study demonstrated an increase in platelets count and a decrease in endotoxin levels in 13 patients with alcoholic cirrhosis receiving rifaximin for a 4-wk course, compared to 10 controls[75]. Even if these results may encourage the use of rifaximin to minimize the complications of endotoxemia due to portal hypertension, larger, randomized, controlled studies extended also to non alcoholic liver disease are required to confirm any clinical efficacy.

RIFAXIMIN SAFETY IN ADVANCED LIVER DISEASE

Rifaximin benefits are generally paralleled by a good safety profile, since the reported rate of adverse events between treated cirrhotics and those who did not receive the drug is similar, and toxicity mainly involves the gastrointestinal tract (*e.g.*, abdominal pain or diarrhea) (Tables 1-3). In particular, nor increase in the rate of infections neither development of antibiotic resistance are common in cirrhotics treated with rifaximin[76,77]. Although some cases of *Clostridium difficile* infection have been reported[51,78], the incidence is comparable to that observed in patients with advanced liver disease and is affected by confounding factors, such as age, repeated hospitalizations, ongoing therapy with proton pump inhibitors and previous courses of antibiotics[78]. *Candida albicans* has also been isolated in fecal samples of about 20% of cirrhotics during rifaximin treatment[65]. Probably, this finding should not be considered unequivocally harmful, since Candida organisms commonly colonize the human gastrointestinal tract as a component of the resident mycobiota[79].

Even if the limited incidence of adverse events has to be attributed to the small amount of rifaximin reaching the systemic circulation, a special consideration regarding its absorption in patients with advanced liver disease is mandatory. Indeed, due to the increased intestinal permeability, higher systemic rifaximin concentrations have been observed in cirrhotics compared to healthy subjects[80]. For this reason, although it may not represent a major problem in the short-term drug administration, the effects of a possible increase in systemic absorption should be cautiously taken into account in cases of prolonged rifaximin administration.

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