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

Ponziani FR *et al.* Rifaximin, gut microbiota and liver cirrhosis

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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 associated 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, generally, 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, to prevent the development of SBP, to reduce endotoxemia in cirrhotics and to improve hemodynamics. These results seem to derive from 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

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**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 SBP 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 really change the overall composition of gut microbiota but that 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-kB expression, exerting anti-inflammatory effects that could counteract the pro-inflammatory response observed in conditions of gut microbiota deregulation[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 gut microbiota composition, which is both quantitative (Small Intestinal Bacterial Overgrowth, SIBO) and qualitative, 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.

**“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 involved in maintaining gastrointestinal health and mainly composed of the phyla Bacteroides 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, increased abundance of Enterobacteriaceae, Streptococcaceae and Veillonellaceae has been reported in cirrhotic patients compared with healthy controls, whereas Lachnospiraceae, Ruminococcaceae, Clostridium clusters XI and XIVab, lactic acid bacteria, Bifidobacteria and *F. prausnitzii* seem to be reduced[40-46].Enterobacterriaeceae family includes *Escherichia coli* (*E.* *coli*) and *Klebsiella spp.*, key bacteria for spontaneous bacterial peritonitis (SBP). Notably, 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 two cases. Further analyses to discriminate the 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 Clostridiae 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 Enterobacteriaceaewith 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 peoples' one[46], it is not surprising that the more the mucosal microbiota resembled that of controls, the better was the cognitive performance and the lower were the serum markers of inflammation in patients with HE[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, 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 change in gut microbiome functionality. Although only patients with minimal HE have been included and some selection biases could be identified, the study by Bajaj *et al* is to date the only published experience reporting the metagenomic and metabolomic changes produced by rifaximin treatment in cirrhotics with 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 (TIPS) 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 has a high prevalence among cirrhotics, ranging between 30% and 70%[38], and it has been associated with the development of SBP due to the translocation of intestinal bacteria to systemic circulation and to the ascitic fluid[66]. Gram-negative bacteria such as *E. 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 have 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 with the 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 *E. 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 and gut microbiota modulation of 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 gradients (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 (HRS), and a better survival compared to controls. Other studies confirmed a reduction in 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 cirrhotic patients. Endotoxemia has been advocated to contribute, together with portal hypertension, in the development of thrombocytopenia in patients with liver cirrhosis[74]. A small preliminary study demonstrated an increase in platelet count and a decrease in endotoxin levels in 13 patients with alcoholic cirrhosis receiving 4 wk of rifaximin treatment, 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 mainly involving the gastrointestinal tract (*e.g.*, abdominal pain or diarrhea) (Tables 1, 2 and 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 *C. difficile* infection have been reported among cirrhotics treated with rifaximin[51,78], the incidence is comparable to that reported 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 is related 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, even if it could not represent a major problem in the short-term drug administration, it is reasonable to take cautiously into account the effects of increased systemic absorption in cases of prolonged rifaximin administration.

**REFERENCES**

1 **Calanni F**, Renzulli C, Barbanti M, Viscomi GC. Rifaximin: beyond the traditional antibiotic activity. *J Antibiot* (Tokyo) 2014; **67**: 667-670 [PMID: 25095806 DOI: 10.1038/ja.2014.106]

2 **Marchese A**, Salerno A, Pesce A, Debbia EA, Schito GC. In vitro activity of rifaximin, metronidazole and vancomycin against Clostridium difficile and the rate of selection of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia-producing species. *Chemotherapy* 2000; **46**: 253-266 [PMID: 10859431 DOI: 10.1159/000007297]

3 **Scarpignato C**, Pelosini I. Rifaximin, a poorly absorbed antibiotic: pharmacology and clinical potential. *Chemotherapy* 2005; **51** Suppl 1: 36-66 [PMID: 15855748 DOI: 10.1159/000081990]

4 **DuPont HL**, Jiang ZD, Ericsson CD, Adachi JA, Mathewson JJ, DuPont MW, Palazzini E, Riopel LM, Ashley D, Martinez-Sandoval F. Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: a randomized, double-blind clinical trial. *Clin Infect Dis* 2001; **33**: 1807-1815 [PMID: 11692292 DOI: 10.1086/323814]

5 **Taylor DN**, Bourgeois AL, Ericsson CD, Steffen R, Jiang ZD, Halpern J, Haake R, Dupont HL. A randomized, double-blind, multicenter study of rifaximin compared with placebo and with ciprofloxacin in the treatment of travelers' diarrhea. *Am J Trop Med Hyg* 2006; **74**: 1060-1066 [PMID: 16760520]

6 **Bielaszewska M**, Idelevich EA, Zhang W, Bauwens A, Schaumburg F, Mellmann A, Peters G, Karch H. Effects of antibiotics on Shiga toxin 2 production and bacteriophage induction by epidemic Escherichia coli O104: H4 strain. *Antimicrob Agents Chemother* 2012; **56**: 3277-3282 [PMID: 22391549 DOI: 10.1128/AAC.06315-11]

7 **Jiang ZD**, DuPont HL, La Rocco M, Garey KW. In vitro susceptibility of Clostridium difficile to rifaximin and rifampin in 359 consecutive isolates at a university hospital in Houston, Texas. *J Clin Pathol* 2010; **63**: 355-358 [PMID: 20354207 DOI: 10.1136/jcp.2009.071688]

8 **Blandizzi C**, Viscomi GC, Marzo A, Scarpignato C. Is generic rifaximin still a poorly absorbed antibiotic? A comparison of branded and generic formulations in healthy volunteers. *Pharmacol Res* 2014; **85**: 39-44 [PMID: 24836868 DOI: 10.1016/j.phrs.2014.05.001]

9 **Tandon P**, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. *Clin Gastroenterol Hepatol* 2012; **10**: 1291-1298 [PMID: 22902776 DOI: 10.1016/j.cgh.2012.08.017]

10 **Xu D**, Gao J, Gillilland M, Wu X, Song I, Kao JY, Owyang C. Rifaximin alters intestinal bacteria and prevents stress-induced gut inflammation and visceral hyperalgesia in rats. *Gastroenterology* 2014; **146**: 484-96.e4 [PMID: 24161699 DOI: 10.1053/j.gastro.2013.10.026]

11 **Gao J**, Gillilland MG, Owyang C. Rifaximin, gut microbes and mucosal inflammation: unraveling a complex relationship. *Gut Microbes* 2014; **5**: 571-575 [PMID: 25244596 DOI: 10.4161/gmic.32130]

12 **Ridlon JM**, Alves JM, Hylemon PB, Bajaj JS. Cirrhosis, bile acids and gut microbiota: unraveling a complex relationship. *Gut Microbes* 2013; **4**: 382-387 [PMID: 23851335 DOI: 10.4161/gmic.25723]

13 **Maccaferri S**, Vitali B, Klinder A, Kolida S, Ndagijimana M, Laghi L, Calanni F, Brigidi P, Gibson GR, Costabile A. Rifaximin modulates the colonic microbiota of patients with Crohn's disease: an in vitro approach using a continuous culture colonic model system. *J Antimicrob Chemother* 2010; **65**: 2556-2565 [PMID: 20852272 DOI: 10.1093/jac/dkq345]

14 **Brigidi P**, Swennen E, Rizzello F, Bozzolasco M, Matteuzzi D. Effects of rifaximin administration on the intestinal microbiota in patients with ulcerative colitis. *J Chemother* 2002; **14**: 290-295 [PMID: 12120885 DOI: 10.1179/joc.2002.14.3.290]

15 **Brown EL**, Xue Q, Jiang ZD, Xu Y, Dupont HL. Pretreatment of epithelial cells with rifaximin alters bacterial attachment and internalization profiles. *Antimicrob Agents Chemother* 2010; **54**: 388-396 [PMID: 19858255 DOI: 10.1128/AAC.00691-09]

16 **Vitali B**, Perna F, Lammers K, Turroni S, Gionchetti P, Brigidi P. Immunoregulatory activity of rifaximin associated with a resistant mutant of Bifidobacterium infantis. *Int J Antimicrob Agents* 2009; **33**: 387-389 [PMID: 19097762 DOI: 10.1016/j.ijantimicag.2008.10.007]

17 **Mencarelli A**, Renga B, Palladino G, Claudio D, Ricci P, Distrutti E, Barbanti M, Baldelli F, Fiorucci S. Inhibition of NF-κB by a PXR-dependent pathway mediates counter-regulatory activities of rifaximin on innate immunity in intestinal epithelial cells. *Eur J Pharmacol* 2011; **668**: 317-324 [PMID: 21806984 DOI: 10.1016/j.ejphar.2011.06.058]

18 **Laterza L**, Ianiro G, Scoleri I, Landi R, Bruno G, Scaldaferri F, Gaetani E, Campanale M, Gasbarrini A. Rifaximin for the treatment of diarrhoea-predominant irritable bowel syndrome. *Expert Opin Pharmacother* 2015; **16**: 607-615 [PMID: 25641072 DOI: 10.1517/14656566.2015.1007951]

19 **Pimentel M**, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, Mareya SM, Shaw AL, Bortey E, Forbes WP; TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011; **364**: 22-32 [PMID: 21208106 DOI: 10.1056/NEJMoa1004409]

20 **Schmulson M**, Bielsa MV, Carmona-Sánchez R, Hernández A, López-Colombo A, López Vidal Y, Peláez-Luna M, Remes-Troche JM, Tamayo JL, Valdovinos MA. Microbiota, gastrointestinal infections, low-grade inflammation, and antibiotic therapy in irritable bowel syndrome: an evidence-based review. *Rev Gastroenterol Mex* 2014; **79**: 96-134 [PMID: 24857420 DOI: 10.1016/j.rgmx.2014.01.004]

21 **Cremonini F**, Lembo A. Rifaximin for the treatment of irritable bowel syndrome. *Expert Opin Pharmacother* 2012; **13**: 433-440 [PMID: 22251066 DOI: 10.1517/14656566.2012.651458]

22 **Jigaranu AO**, Nedelciuc O, Blaj A, Badea M, Mihai C, Diculescu M, Cijevschi-Prelipcean C. Is rifaximin effective in maintaining remission in Crohn's disease? *Dig Dis* 2014; **32**: 378-383 [PMID: 24969283 DOI: 10.1159/000358141]

23 **Guslandi M**. Rifaximin in the treatment of inflammatory bowel disease. *World J Gastroenterol* 2011; **17**: 4643-4646 [PMID: 22180705 DOI: 10.3748/wjg.v17.i42.4643]

24 **Prantera C**, Lochs H, Campieri M, Scribano ML, Sturniolo GC, Castiglione F, Cottone M. Antibiotic treatment of Crohn's disease: results of a multicentre, double blind, randomized, placebo-controlled trial with rifaximin. *Aliment Pharmacol Ther* 2006; **23**: 1117-1125 [PMID: 16611272 DOI: 10.1111/j.1365-2036.2006.02879.x]

25 **Shafran I**, Johnson LK. An open-label evaluation of rifaximin in the treatment of active Crohn's disease. *Curr Med Res Opin* 2005; **21**: 1165-1169 [PMID: 16083525 DOI: 10.1185/030079905X53252]

26 **Shafran I**, Burgunder P. Rifaximin for the treatment of newly diagnosed Crohn's disease: a case series. *Am J Gastroenterol* 2008; **103**: 2158-2160 [PMID: 18796124 DOI: 10.1111/j.1572-0241.2008.01982\_16.x]

27 **Campieri M**, Rizzello F, Venturi A. Combination of antibiotic and probiotic treatment is efficacious in prophylaxis of post-operative recurrence of Crohn’s disease: a randomized controlled study vs mesalamine. *Gastroenterology* 2000; **118**: A781

28 **Prantera C**, Lochs H, Grimaldi M, Danese S, Scribano ML, Gionchetti P; Retic Study Group (Rifaximin-Eir Treatment in Crohn's Disease). Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn's disease. *Gastroenterology* 2012; **142**: 473-481.e4 [PMID: 22155172 DOI: 10.1053/j.gastro.2011.11.032]

29 **Guslandi M**, Petrone MC, Testoni PA. Rifaximin for active ulcerative colitis. *Inflamm Bowel Dis* 2006; **12**: 335 [PMID: 16633057 DOI: 10.1097/01.MIB.0000215092.85116.6c]

30 **Gionchetti P**, Rizzello F, Ferrieri A, Venturi A, Brignola C, Ferretti M, Peruzzo S, Miglioli M, Campieri M. Rifaximin in patients with moderate or severe ulcerative colitis refractory to steroid-treatment: a double-blind, placebo-controlled trial. *Dig Dis Sci* 1999; **44**: 1220-1221 [PMID: 10389700]

31 **Cianci R**, Frosali S, Pagliari D, Cesaro P, Petruzziello L, Casciano F, Landolfi R, Costamagna G, Pandolfi F. Uncomplicated diverticular disease: innate and adaptive immunity in human gut mucosa before and after rifaximin. *J Immunol Res* 2014; **2014**: 696812 [PMID: 25133198 DOI: 10.1155/2014/696812]

32 **Boynton W**, Floch M. New strategies for the management of diverticular disease: insights for the clinician. *Therap Adv Gastroenterol* 2013; **6**: 205-213 [PMID: 23634185 DOI: 10.1177/1756283X13478679]

33 **Moretti A**, Spagnolo A, Mangone M, Chiesara F, Aratari A, Papi C, Koch M. [Role of rifaximin in the treatment of colonic diverticular disease]. *Clin Ter* 2012; **163**: 33-38 [PMID: 22362232]

34 **Papi C**, Ciaco A, Koch M, Capurso L. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicentre double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 1995; **9**: 33-39 [PMID: 7766741 DOI: 10.1111/j.1365-2036.1995.tb00348.x]

35 **Latella G**, Pimpo MT, Sottili S, Zippi M, Viscido A, Chiaramonte M, Frieri G. Rifaximin improves symptoms of acquired uncomplicated diverticular disease of the colon. *Int J Colorectal Dis* 2003; **18**: 55-62 [PMID: 12458383 DOI: 10.1007/s00384-002-0396-5]

36 **Colecchia A**, Vestito A, Pasqui F, Mazzella G, Roda E, Pistoia F, Brandimarte G, Festi D. Efficacy of long term cyclic administration of the poorly absorbed antibiotic Rifaximin in symptomatic, uncomplicated colonic diverticular disease. *World J Gastroenterol* 2007; **13**: 264-269 [PMID: 17226906 DOI: 10.3748/wjg.v13.i2.264]

37 **Bajaj JS**, Cox IJ, Betrapally NS, Heuman DM, Schubert ML, Ratneswaran M, Hylemon PB, White MB, Daita K, Noble NA, Sikaroodi M, Williams R, Crossey MM, Taylor-Robinson SD, Gillevet PM. Systems biology analysis of omeprazole therapy in cirrhosis demonstrates significant shifts in gut microbiota composition and function. *Am J Physiol Gastrointest Liver Physiol* 2014; **307**: G951-G957 [PMID: 25258407 DOI: 10.1152/ajpgi.00268.2014]

38 **Giannelli V**, Di Gregorio V, Iebba V, Giusto M, Schippa S, Merli M, Thalheimer U. Microbiota and the gut-liver axis: bacterial translocation, inflammation and infection in cirrhosis. *World J Gastroenterol* 2014; **20**: 16795-16810 [PMID: 25492994 DOI: 10.3748/wjg.v20.i45.16795]

39 **Morgan XC**, Huttenhower C. Meta'omic analytic techniques for studying the intestinal microbiome. *Gastroenterology* 2014; **146**: 1437-1448.e1 [PMID: 24486053 DOI: 10.1053/j.gastro.2014.01.049]

40 **Lu H**, Wu Z, Xu W, Yang J, Chen Y, Li L. Intestinal microbiota was assessed in cirrhotic patients with hepatitis B virus infection. Intestinal microbiota of HBV cirrhotic patients. *Microb Ecol* 2011; **61**: 693-703 [PMID: 21286703 DOI: 10.1007/s00248-010-9801-8]

41 **Wiest R**, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol* 2014; **60**: 197-209 [PMID: 23993913 DOI: 10.1016/j.jhep.2013.07.044]

42 **Wei X**, Yan X, Zou D, Yang Z, Wang X, Liu W, Wang S, Li X, Han J, Huang L, Yuan J. Abnormal fecal microbiota community and functions in patients with hepatitis B liver cirrhosis as revealed by a metagenomic approach. *BMC Gastroenterol* 2013; **13**: 175 [PMID: 24369878 DOI: 10.1186/1471-230X-13-175]

43 **Chen Y**, Yang F, Lu H, Wang B, Chen Y, Lei D, Wang Y, Zhu B, Li L. Characterization of fecal microbial communities in patients with liver cirrhosis. *Hepatology* 2011; **54**: 562-572 [PMID: 21574172 DOI: 10.1002/hep.24423]

44 **Tuomisto S**, Pessi T, Collin P, Vuento R, Aittoniemi J, Karhunen PJ. Changes in gut bacterial populations and their translocation into liver and ascites in alcoholic liver cirrhotics. *BMC Gastroenterol* 2014; **14**: 40 [PMID: 24564202 DOI: 10.1186/1471-230X-14-40]

45 **Zhang Z**, Zhai H, Geng J, Yu R, Ren H, Fan H, Shi P. Large-scale survey of gut microbiota associated with MHE Via 16S rRNA-based pyrosequencing. *Am J Gastroenterol* 2013; **108**: 1601-1611 [PMID: 23877352 DOI: 10.1038/ajg.2013.221]

46 **Bajaj JS**, Betrapally NS, Hylemon PB, Heuman DM, Daita K, White MB, Unser A, Thacker LR, Sanyal AJ, Kang DJ, Sikaroodi M, Gillevet PM. Salivary microbiota reflects changes in gut microbiota in cirrhosis with hepatic encephalopathy. *Hepatology* 2015; Epub ahead of print [PMID: 25820757 DOI: 10.1002/hep.27819]

47 **Qin N**, Yang F, Li A, Prifti E, Chen Y, Shao L, Guo J, Le Chatelier E, Yao J, Wu L, Zhou J, Ni S, Liu L, Pons N, Batto JM, Kennedy SP, Leonard P, Yuan C, Ding W, Chen Y, Hu X, Zheng B, Qian G, Xu W, Ehrlich SD, Zheng S, Li L. Alterations of the human gut microbiome in liver cirrhosis. *Nature* 2014; **513**: 59-64 [PMID: 25079328 DOI: 10.1038/nature13568]

48 **Bajaj JS**, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, Noble NA, Unser AB, Daita K, Fisher AR, Sikaroodi M, Gillevet PM. Altered profile of human gut microbiome is associated with cirrhosis and its complications. *J Hepatol* 2014; **60**: 940-947 [PMID: 24374295 DOI: 10.1016/j.jhep.2013.12.019]

49 **Bajaj JS**, Ridlon JM, Hylemon PB, Thacker LR, Heuman DM, Smith S, Sikaroodi M, Gillevet PM. Linkage of gut microbiome with cognition in hepatic encephalopathy. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G168-G175 [PMID: 21940902 DOI: 10.1152/ajpgi.00190.2011]

50 **Bajaj JS**, Hylemon PB, Ridlon JM, Heuman DM, Daita K, White MB, Monteith P, Noble NA, Sikaroodi M, Gillevet PM. Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G675-G685 [PMID: 22821944 DOI: 10.1152/ajpgi.00152.2012]

51 **Bass NM**, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, Sigal S, Sheikh MY, Beavers K, Frederick T, Teperman L, Hillebrand D, Huang S, Merchant K, Shaw A, Bortey E, Forbes WP. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; **362**: 1071-1081 [PMID: 20335583 DOI: 10.1056/NEJMoa0907893]

52 **Neff GW**, Jones M, Broda T, Jonas M, Ravi R, Novick D, Kaiser TE, Kemmer N. Durability of rifaximin response in hepatic encephalopathy. *J Clin Gastroenterol* 2012; **46**: 168-171 [PMID: 22011586 DOI: 10.1097/MCG.0b013e318231faae]

53 **Sharma BC**, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol* 2013; **108**: 1458-1463 [PMID: 23877348 DOI: 10.1038/ajg.2013.219]

54 **Maharshi S**, Sharma BC, Srivastava S, Jindal A. Randomised controlled trial of lactulose versus rifaximin for prophylaxis of hepatic encephalopathy in patients with acute variceal bleed. *Gut* 2015; **64**: 1341-1342 [PMID: 25320105 DOI: 10.1136/gutjnl-2014-308521]

55 **Sharma K**, Pant S, Misra S, Dwivedi M, Misra A, Narang S, Tewari R, Bhadoria AS. Effect of rifaximin, probiotics, and l-ornithine l-aspartate on minimal hepatic encephalopathy: a randomized controlled trial. *Saudi J Gastroenterol* 2014; **20**: 225-232 [PMID: 25038208 DOI: 10.4103/1319-3767.136975]

56 **Mas A**, Rodés J, Sunyer L, Rodrigo L, Planas R, Vargas V, Castells L, Rodríguez-Martínez D, Fernández-Rodríguez C, Coll I, Pardo A. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. *J Hepatol* 2003; **38**: 51-58 [PMID: 12480560]

57 **Paik YH**, Lee KS, Han KH, Song KH, Kim MH, Moon BS, Ahn SH, Lee SJ, Park HJ, Lee DK, Chon CY, Lee SI, Moon YM. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. *Yonsei Med J* 2005; **46**: 399-407 [PMID: 15988813]

58 **Leevy CB**, Phillips JA. Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy. *Dig Dis Sci* 2007; **52**: 737-741 [PMID: 17245628]

59 **Bajaj JS**, Heuman DM, Wade JB, Gibson DP, Saeian K, Wegelin JA, Hafeezullah M, Bell DE, Sterling RK, Stravitz RT, Fuchs M, Luketic V, Sanyal AJ. Rifaximin improves driving simulator performance in a randomized trial of patients with minimal hepatic encephalopathy. *Gastroenterology* 2011; **140**: 478-487.e1 [PMID: 20849805 DOI: 10.1053/j.gastro.2010.08.061]

60 **Sanyal A**, Younossi ZM, Bass NM, Mullen KD, Poordad F, Brown RS, Vemuru RP, Mazen Jamal M, Huang S, Merchant K, Bortey E, Forbes WP. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2011; **34**: 853-861 [PMID: 21848797 DOI: 10.1111/j.1365-2036.2011.04808.x]

61 **Sidhu SS**, Goyal O, Mishra BP, Sood A, Chhina RS, Soni RK. Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial). *Am J Gastroenterol* 2011; **106**: 307-316 [PMID: 21157444 DOI: 10.1038/ajg.2010.455]

62 **Bajaj JS**, Heuman DM, Sanyal AJ, Hylemon PB, Sterling RK, Stravitz RT, Fuchs M, Ridlon JM, Daita K, Monteith P, Noble NA, White MB, Fisher A, Sikaroodi M, Rangwala H, Gillevet PM. Modulation of the metabiome by rifaximin in patients with cirrhosis and minimal hepatic encephalopathy. *PLoS One* 2013; **8**: e60042 [PMID: 23565181 DOI: 10.1371/journal.pone.0060042]

63 **Wang CC**, Kao JH. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; **362**: 2423; author reply 2424-2425 [PMID: 20573932 DOI: 10.1056/NEJMc1004719]

64 **Zullo A**, Hassan C, Lorenzetti R. Rifaximin therapy in minimal hepatic encephalopathy cirrhotics. *Am J Gastroenterol* 2011; **106**: 2041; author reply 2041-2042 [PMID: 22056578 DOI: 10.1038/ajg.2011.216]

65 **Zullo A**, Hassan C, Ridola L, Lorenzetti R, Campo SM, Riggio O. Rifaximin therapy and hepatic encephalopathy: Pros and cons. *World J Gastrointest Pharmacol Ther* 2012; **3**: 62-67 [PMID: 22966484 DOI: 10.4292/wjgpt.v3.i4.62]

66 **Hanouneh MA**, Hanouneh IA, Hashash JG, Law R, Esfeh JM, Lopez R, Hazratjee N, Smith T, Zein NN. The role of rifaximin in the primary prophylaxis of spontaneous bacterial peritonitis in patients with liver cirrhosis. *J Clin Gastroenterol* 2012; **46**: 709-715 [PMID: 22878533 DOI: 10.1097/MCG.0b013e3182506dbb]

67 **Rogers GB**, Russell LE, Preston PG, Marsh P, Collins JE, Saunders J, Sutton J, Fine D, Bruce KD, Wright M. Characterisation of bacteria in ascites--reporting the potential of culture-independent, molecular analysis. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 533-541 [PMID: 20238135 DOI: 10.1007/s10096-010-0891-5]

68 **Rogers GB**, van der Gast CJ, Bruce KD, Marsh P, Collins JE, Sutton J, Wright M. Ascitic microbiota composition is correlated with clinical severity in cirrhosis with portal hypertension. *PLoS One* 2013; **8**: e74884 [PMID: 24086392 DOI: 10.1371/journal.pone.0074884]

69 **Lutz P**, Parcina M, Bekeredjian-Ding I, Nischalke HD, Nattermann J, Sauerbruch T, Hoerauf A, Strassburg CP, Spengler U. Impact of rifaximin on the frequency and characteristics of spontaneous bacterial peritonitis in patients with liver cirrhosis and ascites. *PLoS One* 2014; **9**: e93909 [PMID: 24714550 DOI: 10.1371/journal.pone.0093909]

70 **Guarner C**, Runyon BA, Heck M, Young S, Sheikh MY. Effect of long-term trimethoprim-sulfamethoxazole prophylaxis on ascites formation, bacterial translocation, spontaneous bacterial peritonitis, and survival in cirrhotic rats. *Dig Dis Sci* 1999; **44**: 1957-1962 [PMID: 10548343]

71 **Vlachogiannakos J**, Saveriadis AS, Viazis N, Theodoropoulos I, Foudoulis K, Manolakopoulos S, Raptis S, Karamanolis DG. Intestinal decontamination improves liver haemodynamics in patients with alcohol-related decompensated cirrhosis. *Aliment Pharmacol Ther* 2009; **29**: 992-999 [PMID: 19210289 DOI: 10.1111/j.1365-2036.2009.03958.x]

72 **Vlachogiannakos J**, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *J Gastroenterol Hepatol* 2013; **28**: 450-455 [PMID: 23216382 DOI: 10.1111/jgh.12070]

73 **Kalambokis GN**, Tsianos EV. Rifaximin reduces endotoxemia and improves liver function and disease severity in patients with decompensated cirrhosis. *Hepatology* 2012; **55**: 655-656 [PMID: 22030839 DOI: 10.1002/hep.24751]

74 **Kalambokis G**, Tsianos EV. Endotoxaemia in the pathogenesis of cytopenias in liver cirrhosis. Could oral antibiotics raise blood counts? *Med Hypotheses* 2011; **76**: 105-109 [PMID: 20832949 DOI: 10.1016/j.mehy.2010.08.043]

75 **Kalambokis GN**, Mouzaki A, Rodi M, Tsianos EV. Rifaximin improves thrombocytopenia in patients with alcoholic cirrhosis in association with reduction of endotoxaemia. *Liver Int* 2012; **32**: 467-475 [PMID: 22098272 DOI: 10.1111/j.1478-3231.2011.02650.x]

76 **Mullen KD**, Sanyal AJ, Bass NM, Poordad FF, Sheikh MY, Frederick RT, Bortey E, Forbes WP. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. *Clin Gastroenterol Hepatol* 2014; **12**: 1390-7.e2 [PMID: 24365449 DOI: 10.1016/j.cgh.2013.12.021]

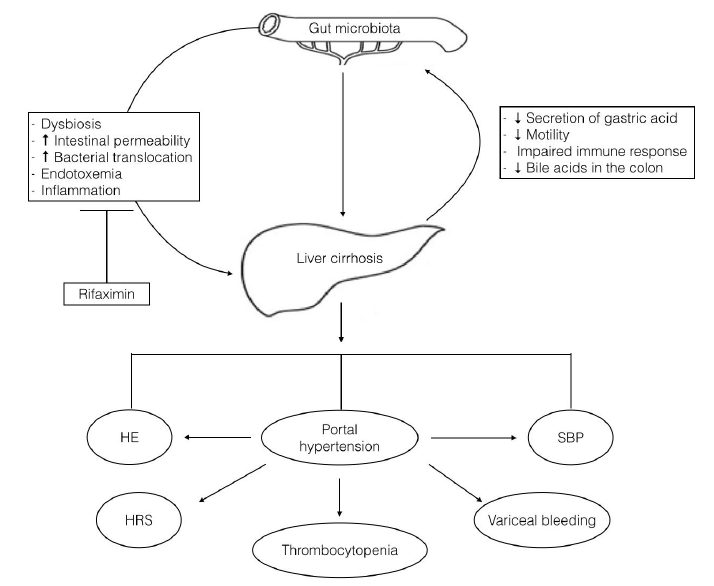
77 **Bajaj JS**, Barrett AC, Bortey E, Paterson C, Forbes WP. Prolonged remission from hepatic encephalopathy with rifaximin: results of a placebo crossover analysis. *Aliment Pharmacol Ther* 2015; **41**: 39-45 [PMID: 25339518 DOI: 10.1111/apt.12993]

78 **Vanjak D**, Girault G, Branger C, Rufat P, Valla DC, Fantin B. Risk factors for Clostridium difficile infection in a hepatology ward. *Infect Control Hosp Epidemiol* 2007; **28**: 202-204 [PMID: 17265403]

79 **Kumamoto CA**. Inflammation and gastrointestinal Candida colonization. *Curr Opin Microbiol* 2011; **14**: 386-391 [PMID: 21802979 DOI: 10.1016/j.mib.2011.07.015]

80 **Bajaj JS**, Riggio O. Drug therapy: rifaximin. *Hepatology* 2010; **52**: 1484-1488 [PMID: 20814894 DOI: 10.1002/hep.23866]

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**Figure 1 Effects of Rifaximin on gut-liver axis.** Rifaximin decreases endotoxemia and inflammation both directly and indirectly, by reducing bacterial translocation. Moreover, it counteracts bacterial overgrowth and is able to modulate gut microbiome functionality. Due to these characteristics, 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.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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** | **N 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/daily 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 versus 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/daily 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 to 1600 mg/daily)  54 pts rifaximin (600 to 1200 mg/daily) + lactulose (90 mL/daily) 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 shift in the gut microbiome functionality | 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/daily  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. pts** | **Disease severity** | **Disease complication** | **Treatment schedule** | **Results** | **Safety** |
| Hanouneh[66] *et al* 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** | **N pts** | **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/daily for 28 d | Median (range) plasma endotoxin levels decreased significantly after rif-  aximin 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-week course of rifaximin  (1200 mg/d)  Rifaximin 1200 mg/daily for 8 wk | Rifaximin signiﬁcantly reduced plasma endotoxin lev-  els  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 (see reference[71])  46 cirrhotic controls | Median (range) plasma endotoxin levels decreased significantly after rif-  aximin 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/daily 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.