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TOPIC HIGHLIGHT

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Gut microbiota-related complications in cirrhosis

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Abstract

Gut microbiota plays an important role in cirrhosis. The liver is constantly challenged with commensal bacteria and their products arriving through the portal vein in the so-called gut-liver axis. Bacterial translocation from the intestinal lumen through the intestinal wall and to mesenteric lymph nodes is facilitated by intestinal bacterial overgrowth, impairment in the permeability of the intestinal mucosal barrier, and deficiencies in local host immune defences. Deranged clearance of endogenous bacteria from portal and systemic circulation turns the gut into the major source of bacterial-related complications. Liver function may therefore be affected by alterations in the composition of the intestinal microbiota and a role for commensal flora has been evidenced in the pathogenesis of several complications arising in end-stage liver disease such as hepatic encephalopathy, splanchnic arterial vasodilatation and spontaneous bacterial peritonitis. The use of antibiotics is the main therapeutic pipeline in the management of these bacteria-related complications. However, other strategies aimed at preserving intestinal homeostasis through the use of pre-, pro- or symbiotic formulations are being studied in the last years. In this review, the role of intestinal microbiota in the development of the most frequent complications arising in cirrhosis and the different clinical and experimental studies conducted to prevent or improve these complications by modifying the gut microbiota composition are summarized.

Key words: Cirrhosis; Encephalopathy; Portal hypertension; Spontaneous bacterial peritonitis; Microbiota; Bacterial translocation

Core tip: The close relationship between the most frequent complications arising in patients with cirrhosis and the gut microbiota has been intensively studied in the last years and has enhanced the relevance of the constant communication between the gut and the liver in the management of patients with cirrhosis. This review intends to integrate the existing knowledge of the role of intestinal microbiota plays in the development of these complications and the evidence on the possible efficacy of gut-microbiota modulating strategies to help in their management.

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INTRODUCTION

Cirrhosis is the common end-stage liver histologic distortion for several hepatic diseases, characterized by the presence of regenerative nodules that causes portal hy-

pertension. This fact in turn alters intestinal motility inducing intestinal bacterial overgrowth (IBO)[1]. The close relationship between the most frequent complications arising in patients with cirrhosis and the gut microbiota has been intensively studied in the last years and has enhanced the relevance of the constant communication between the gut and the liver in the management of patients with cirrhosis[2]. Complications such as hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP) and variceal bleeding are directly caused or aggravated by the translocation of enteric bacteria or their products into the blood of cirrhotic patients.

The current pathogenic mechanism to explain the passage of bacteria or their products from the intestinal lumen through the intestinal barrier and to mesenteric lymph nodes is defined as bacterial translocation (BT)[3,4]. IBO, impairment in intestinal permeability, and deficiencies in local host immune defences are the major mechanisms postulated to favour BT in cirrhosis[5,6]. Any of these abnormalities deranges clearance of endogenous bacteria from portal and systemic circulation, turning the gut into the major source of bacterial-related complications.

The large bowel is the most densely populated natural environment known, containing roughly 10^{14} bacterial cells[7], which represents around ten times more microbial cells than eukaryotic cells. Gut microbiota is a large and diverse population of living microorganisms (approximately 500-1500 different bacterial species[8]), susceptible to environmental and pathophysiological alterations[9]. Original studies on mice showed that gastrointestinal microbiota is mainly composed by *Enterobacteriaceae*, *Lactobacillus*, *Bacteroides* and *Clostridium*[10,11]. More recent studies using next generation sequencing techniques (NGS) that allow a deeper analysis of the microbiota have reveled alterations in phylotypes previously overlooked using conventional techniques in patients with liver cirrhosis[12,13].

These experimental studies have brought the attention of clinicians to new therapeutic strategies targeting gut microbiota composition and function and aimed at preventing BT episodes and inflammation in cirrhosis. In fact, a recent publication by Kakiyama *et al*[14] provides interesting data in which among other reasons, dysbiosis is occurring in patients with cirrhosis in part due to low bile acid input into the gut. In this regard, prebiotics, probotics or symbiotics have been evaluated in different clinical studies in the last years[15].

This review intends to integrate the existing knowledge of the role of intestinal microbiota plays in the development of the most frequent complications arising in cirrhosis and the evidence on the possible efficacy of gut-microbiota modulating strategies to help in the management of these complications.

HE

HE is a serious and progressive neuropsychiatric condition that occurs in patients with advanced cirrhosis. Overt HE presents as a wide spectrum of clinical signs and symptoms, ranging in severity from mild confusion to life-threatening coma. Minimal HE is a more subtle form of the condition; it is characterized by deficits in cognitive function that can be detected with specialized tools. HE is considered to complicate up to 25% of presentations of acute liver failure[16], and is associated with poor survival[17,18].

Ammonia is a key factor in the pathogenesis of HE in cirrhotic patients[19]. The association between ammonia neurotoxicity and HE was first suggested by studies in dogs with porto-cava anastomosis[20]. Ammonia is generated in the intestines from dietary nitrogen, primarily from the breakdown of urea by urease present in colonic microbiota[21]. Under normal conditions, ammonia is metabolized to urea in the liver, but in the setting of liver failure, ammonia can bypass the liver into systemic circulation, inducing oxidative stress by generation of free radicals, and the nitrotyrosination of proteins in the brain[22]. This process is critical for mithochondrial function, and may cause failure of normal neurotransmission. Ammonia is taken up by astrocytes in the brain, and converted to glutamine where it exerts an osmotic effect and result in astrocyte swelling and brain edema[23-25].

Several studies show that gut microbiota is altered in cirrhotic patients with HE. More specifically, a quantitative change in the Bacteroides/Firmicutes ratio, with the prevalence of potentially pathogenic bacteria (*e.g.*, *Enterobacteriaceae*)[13,26] and the reduction of commensals (*Lachnospiraceae*)[26] have been described. Liu *et al*[27] demonstrated a significant fecal overgrowth of potentially pathogenic *Escherichia coli* (*E. coli*) and *Staphylococcus spp*. in the gut microbiota of cirrhotic patients with minimal HE. Other studies have shown that patients with cirrhosis and HE had higher concentration of *Enterobacteriaceae* and *Alcaligenaceae* compared with control subjects and cirrhotic patients without HE[26]. This study shows, as well, that specific bacterial families (*Alcaligenaceae*, *Porphyromonadaceae*, *Enterobacteriaceae*) are strongly associated with cognition and inflammation in HE[26]. Bajaj *et al*[26,28,29] also studied the relationship between gut microbiota, inflammation and cognition in cirrhotic patients. Increased *Alcaligenaceae* abundance was significantly associated with poor cognitive performance, whereas *Enterobacteriaceae* were associated with worsening inflammation in the cirrhosis group. *Alcaligenaceae* are Proteobacteria that degrade urea to produce ammonia, which may explain his association with poor cognitive function[30]. Finally, in patients with HE, markers of Th17 and immune response were highly correlated with gut microbiome components, possibly indicating a synergy between inflammation and cognition with microbiome changes[31,32]. This evidence supports previous data revealing the components of the gut microbiota are required for the differentiation of Th17 cells in mouse models of autoimmune disease[33].

Treatment of HE is based in part on manipulation of the gut microbiota[34], with the aim to decrease the production and intestinal absorption of ammonia[35]. Lactulose (4-O-β-d-galactopyranosyl-d-fructose) is the most widely used treatment in HD; it lowers the colonic pH as a result of the production of organic acids by bacterial

fermentation, inducing an environment that is both hostile to the survival of urease-producing gut bacteria, such as *Klebsiella* spp. and *Proteus* spp, facilitating the growth of acid resistant, non-urease-producing species, such as lactobacilli and bifidobacteria. This approach firstly reduces the ammonia production in the colonic lumen and secondly the acidification of colonic environment reduces the absorption of ammonia by nonionic diffusion[35].

Rifaximin is a non-absorbable antibiotic that is known that improve cognitive function in HE, especially its subclinical form, minimal HE, but the precise mechanism of its action is unclear[36]. A recent clinical trial by Bajaj *et al*[36] demonstrates that rifaximin is associated with reduction in endotoxemia in patients with cirrhosis and minimal HE, with a modest change in the stool microbiota composition, reducing *Veillonellaceae* and increasing *Eubacteriaceae*. After rifaximin therapy, there was also a significant change in the serum metabolome characterized by a specific increase in serum fatty acids. Although rifaximin is more effective than lactulose in the maintenance of remission and decreased re-admission in patients with minimal HE, it was not as cost-effective as lactulose[37].

The administration of probiotics that may modulate the gut microbiota composition or function in HE has had as primary objective to reduce the total amount of ammonia that reaches the portal system; this effect can be mediated through various mechanisms[38]. Several studies have shown the efficacy of some probiotics in the treatment of minimal HE and the prevention of overt HE episodes[39]. The first studies with probiotics in patients with cirrhosis and HE[40,41], compared the effects of administration of *Enterococcus faecium* SF68 *vs* lactulose on ammoniemia and clinical scores of HE. In these randomized studies, the probiotic SF68 showed similar results to lactulose during the treatment period. The therapeutic effect was maintained even during the washout period but only in the group treated with probiotics, suggesting that SF68 transiently colonize the colon and, consequently, this could favor the persistence of the effects.

In a prospective, randomized controlled trial, probiotics (including strains of the species *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*, 110 billion CFU, available as VSL#3) were found to be effective in preventing HE in patients with cirrhosis[42]. However, in a double-blind placebo-controlled study that included patients with cirrhosis and at least one major complication of cirrhosis in the past, probiotic supplementation did not show beneficial effects on portal hypertension or decreased hepatic synthetic function, in patients with compensated cirrhosis[43]. Nevertheless, results pointed toward a possible positive effect of this probiotic in patients with above normal baseline ammonia levels.

An interesting study in rats with experimental cirrhosis demonstrated that a strain of the probiotic *Lactobacillus plantarum* is able to decrease amoniemia[44]. Considering the importance of ammonia in the pathogenesis of HE[45], this study suggests that treatment with this probiotic may be useful in patients with cirrhosis to treat or prevent this complication. Also, several studies[27,46-48] have yielded interesting results with synbiotics both in presence of overt HE, but also in minimal HE, as detected by improvement of all psychometric evaluations. However, the correlation between ammonia concentration and HE severity in patients with cirrhosis of liver is still poor[49]. Actually, it is common to find patients with symptoms of overt HE with just moderately elevated arterial ammonia levels[50]. This is probably related to the fact that HE is believed to be the consequence of different disturbances developed in advanced cirrhosis, and not only of hyperammoniemia[51,52].

SPLANCHNIC ARTERIAL VASODILATION

Splanchnic arterial vasodilation is the principal factor in the pathogenesis of the hyperdynamic circulatory syndrome that occurs in patients with cirrhosis and portal hypertension[53-55]. Increased synthesis and vascular release of the potent vasodilator nitric oxide (NO) is considered to be its main cause. Activation of the endothelial and inducible forms of nitric oxide synthase (eNOS and iNOS respectively) are considered to be the main sources of the elevated levels of NO in the splanchnic circulation. While activation of eNOS is due mostly to shear stress, exposure to bacteria and their products, directly or involving host cytokines, has been associated with activation of iNOS and increased release of NO[56] which in turn exacerbates further the circulatory disarrangement of cirrhosis[57,58]. TNF-α is also known to be involved in the pathogenesis of the hyperdynamic circulatory syndrome in portal hypertension[59,60].

Esophageal varices develop in response to the portal hypertension. Compared with other collaterals, gastroesophageal varices are important because of their risk of rupture and bleeding. Esophageal variceal bleeding is a serious event with 30% mortality per episode, and the likelihood of rebleeding reaches 30% to 40% in the first 6 wk without adequate therapy.

The management of variceal bleeding requires a complex approach[61] including vaso-pressors[62], use of prophylactic antibiotics[63,64], emergency endoscopic therapy[65,66], access to salvage therapy with trans-jugular intrahepatic portosystemic shunting (TIPS) in the most severe cases[67], as well as improvements in general supportive and critical care.

The use of prophylactic antibiotics (norfloxacin or ceftriaxone) in the setting of acute variceal bleeding is standard practice because it is known that decreases the rate of bacterial infection, risk of early rebleeding, and mortality[68,69]. However, antibiotic prophylaxis is associated with risk of infection with multi-resistant strains. The effect of the quinolone on the enteric bacterial load not only decreases the risk of bacterial infections but also increases systemic vascular resistance, improving haemodynamics[70].

Studies have suggested that chronic manipulation of the intestinal microbiota could have beneficial effects

on the treatment of portal hypertension, but a few studies[37,43,71-73] have investigated the administration of probiotics to patients with variceal bleeding. In an experimental model of pre-hepatic portal hypertension[73], bacteriotherapy with a strain of *Lactobacillus acidophilus* or *Lactobacillus* GG. did not cause significant changes in BT between the animals treated with probiotic (82%) and those treated with placebo (75%), probably because of their ineffectivenes to modulate the microbiota composition.

In general no portal hypotensive effect has been observed when administering probiotics. In two different studies[74,75], the VSL#3 probiotic (a mix of lactic acid bacteria) used in patients with compensated or early decompensated cirrhosis and hepatic venous pressure gradient > 10 mmHg, resulted in no reduction in portal pressure. In one of them though[75], probiotic administration helped to decrease plasma endotoxin that suggests possible beneficial effects of probiotics for this patient population. In a recent study performed in cirrhotic patients having large esophageal varices without history of variceal bleeding[71], adjunctive probiotic VSL#3 improved the response rate to propranolol therapy and was safe and well tolerated in patients with cirrhosis. A double-blind placebo-controlled study that included patients with liver cirrhosis and at least one major complication of cirrhosis in the past (like variceal bleeding), and where the participants were randomly assigned to receive different probiotic capsules or placebo[43], did not show any significant clinical or laboratory effect of probiotic administration in patients with cirrhosis.

SBP

Bacterial infections are a frequent complication in patients with decompensated cirrhosis, with an incidence at the time of admission or during the hospitalization of about 32% in the most recent prospective studies[76]. Among them, SBP is the most common type of infection, induced in up to 70%-80% of cases by aerobic Gram-negative enteric organism, mainly *E. coli* and *Klebsiella pneumoniae*[77-79]. SBP is the infection of ascitic fluid in the absence of any primary intra-abdominal source, and it is considered to be present if the ascitic neutrophil count is in excess of 250 per microliter[69], with either positive or negative microbiological culture[79,80].

Broad-spectrum intravenous antibiotic therapy should be commenced immediately after diagnosed paracentesis in patients in whom SBP is clinically suspected or after the demonstration of a raised ascitic neutrophil count, without waiting for the result of the culture. SBP is usually treated with antibiotics using third generation cephalosporins. Cefotaxime or similar third-generation cephalosporin for a total course of 5 d is the treatment of choice[81-84]. Oral ofloxacin has been shown in one randomized controlled trial to be as effective as intravenous cefotaxime for a subgroup of patients with SBP and absence of risk factors[85]. Ciprofloxacin or levofloxacin can be used in patients who are intolerant to beta lactams. Patients surviving a SBP episode have a recurrence rate at 1 year of approximately 70%. In this setting indefinite selective intestinal decontamination with oral Norfloxacin reduces the risk of SBP recurrence from 50% to 20% at 2 years[86].

An increased frequency of infections due to quinolone-resistant (either Gram positive or negative) and multiresistant bacteria has recently been recognized though in patients being treated with norfloxacin, and this is associated with failure to control the infection with empiric antibiotic therapy and increased mortality[87]. New alternative strategies are needed for the empirical prophylaxis of nosocomial infections in cirrhosis. There have been several studies looking for alternative therapies to the use of Norfloxacin in high-risk patients with cirrhosis. In an experimental model in rats with CCl4-induced cirrhosis, long-term prophylactic trimethoprim-sulfamethoxazole administration delayed the development of ascites and reduced the incidence of Gram-negative bacteria translocation, without increasing Gram-positive episodes, suggesting that trimethoprim-sulfamethoxazole might be a good alternative to norfloxacin[88]. Another study showed that ciprofloxacin administered in a weekly dose was ineffective in selective intestinal decontamination, and was not useful in preventing SBP[89]. Rifaximin has been shown to decrease portal-hypertension related complications in a prospective randomized trial[90]. Taken together, available information suggests that blockade of episodes of BT by using oral antibiotics decreases the risk of development of different types of complications, and not only infections. Their use though, predisposes patients to develop infections by QR and MR bacteria. New therapeutic options are needed.

Proinflammatory cytokines are involved in the process of BT. Administration of anti TNF has been shown to significantly decrease BT in a rat model of cirrhosis[91]. This approach however has not been pursued further for the risk of inducing infections. Pentoxyfilline is also an anti TNF drug that has been shown to have a similar efficacy to norfloxacin in the prevention of BT and SBP in rats with CCl_4-induced cirrhosis and ascites[92]. This is in line with an experimental study in CCl_4-induced cirrhosis in rats showing that a prolonged oxidative stress in the intestine, accompanied by changes in gut microbiota composition, might facilitate translocation across the mucosa, resulting in complications such as SBP[93]. In fact, pentoxifylline administration, but not norfloxacin, decreases oxidative stress in cecal mucosa.

Probiotics appear therefore as attractive alternatives to antibiotics. They are often components of the commensal intestinal microbiota and have been shown to exert a number of beneficial effects mainly in animal models and to a lesser extent in humans. Results reported in the literature are still conflicting regarding efficacy. In a rat model of experimental CCl_4-induced cirrhosis and ascites[94], *Lactobacillus* GG was unable to prevent both BT and infection of the ascitic fluid. In another study using *Lactobacillus johnsonii* (*L. johnsonii*) LA1 with antioxidants[95] in rats with CCl_4-induced cirrhosis, there was a decrease in intestinal enterobacteria and in BT compared to un-

treated control rats, and there was a reduction in malonyldialdehyde (MDA) levels, an index of intestinal oxidative damage; however, in this study, the probiotic was not administered in the absence of antioxidants to be able to attribute a role to the probiotic *per se*. A recent work using the same animal model without antioxidants[96], indicate that *L. johnsonii* La1 alone has no significant effect on intestinal microbiota and BT in this experimental model of cirrhosis. The present data suggest that the beneficial effects observed in the previous study were mainly due to the antioxidant effect of vitamin C and glutamate.

A double-blind, randomized-controlled trial was conducted in cirrhotic patients who had either recovered from SBP (secondary prophylaxis) or who were at a high risk for the development of SBP[97] to assess the efficacy of administration of probiotics as secondary prophylaxis of infections. Norfloxacin (400 mg/d) with probiotic capsules (strains of *Enterococcus faecalis*, *Clostridium butyricum*, *Bacillus mesentericus* JPC, *Bacillus coagulans*) or norfloxacin with a placebo were given and the occurrence of SBP within a period of 6 mo, and side effects of therapy and mortality were recorded. Results were similar between groups, showing that the addition of probiotics to norfloxacin does not improve its efficacy in primary or secondary prophylaxis of SBP or in reducing the mortality in cirrhotic patients with ascites.

Stadlbauer *et al*[98] observed that treatment with *Lactobacillus casei Shirota* in cirrhotic patients of alcoholic etiology improved the phagocytic activity of neutrophils, decreased the levels of soluble TNF receptor 1 and 2 after stimulation with endotoxin and decreased overexpression of TLR4, indicating that the beneficial effect of the probiotic would result, at least in part, from the modification of the antigenic stimulus and IL10 secretion.

Recently, our group has evaluated the effects of *Bifidobacterium pseudocatenulatum* CECT7765 on BT and the liver status in a experimental model of cirrhosis in Balb/c mice by oral administration of CCl_4, resulting in an improved gut barrier integrity and showing a beneficial effect against induced bacterial antigen translocation with *E. coli*[99].

CONCLUSION

As reviewed here, many studies have demonstrated the relevance of the interaction between the gut and the liver in the development of bacteria-related complications in cirrhosis. Changes in the microbiota composition have been shown to disturb intestinal immune homeostasis, which plays a central role in the proper management of the host-microbe crosstalk, not only favouring the translocation of pro-inflammatory bacterial products but also impairing the immunological host defence mechanisms against them and facilitating the production of soluble mediators that further complicate the liver disease.

While the use of antibiotics continues being an effective strategy for the management of these complications, other alternatives have emerged in the attempt to avoid the adverse impact of antibiotic therapy on the microbiota composition and function, given its relevance in keeping the intestinal homeostasis. These strategies include the use of pre-, pro- or synbiotic formulations, and experimental faecal transplantation aimed at restoring a "healthier" microbiota environment in patients with decompensated cirrhosis. Nevertheless, in contrast to abundant clinical evidence of efficacy and safety of the use of antibiotics in these patients, data available regarding the efficacy of these other strategies mainly comes from individual experimental studies[100]. The results of ongoing research in this area and the design of further studies on alternative microbiota-based interventions to prevent or to modulate bacteria-related complications in cirrhosis will shed light into the intimate interaction between the gut and the liver that lay down the development of these complications and into the design of more efficient strategies to re-shape the microbiota.

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