Review

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The microbiota in cirrhosis and its role in hepatic decompensation

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Summary

Cirrhosis – the common end-stage of chronic liver disease – is associated with a cascade of events, of which intestinal bacterial overgrowth and dysbiosis are central. Bacterial toxins entering the portal or systemic circulation can directly cause hepatocyte death, while dysbiosis also affects gut barrier function and increases bacterial translocation, leading to infections, systemic inflammation and vasodilation, which contribute to acute decompensation and organ failure. Acute decompensation and its severe forms, pre-acute-on-chronic liver failure (ACLF) and ACLF, are characterised by sudden organ dysfunction (and failure) and high short-term mortality. Patients with pre-ACLF and ACLF present with high-grade systemic inflammation, usually precipitated by proven bacterial infection and/or severe alcoholic hepatitis. However, no precipitant is identified in 30% of these patients, in whom bacterial translocation from the gut microbiota is assumed to be responsible for systemic inflammation and decompensation. Different microbiota profiles may influence the rate of decompensation and thereby outcome in these patients. Thus, targeting the microbiota is a promising strategy for the prevention and treatment of acute decompensation, pre-ACLF and ACLF. Approaches include the use of antibiotics such as rifaximin, faecal microbial transplantation and enterosorbents (*e.g.* Yaq-001), which bind microbial factors without exerting a direct effect on bacterial growth kinetics. This review focuses on the role of microbiota in decompensation and strategies targeting microbiota to prevent acute decompensation.

Keywords: Acute-on-chronic liver failure; Acute decompensation; Cirrhosis; Gut-liver-axis; Portal hypertension.

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Introduction

Cirrhosis is the result of many years of chronic liver disease (CLD).[1] Often silent, CLD slowly changes the liver by restructuring its architecture, combining wound-healing processes, such as remodelling and fibrosis, with a decrease in the functioning parenchymal mass, which eventually leads to cirrhosis.[2] In cirrhosis, which is also silent for years, the whole organism (skin, brain, kidneys, gastrointestinal tract, immune system, bone marrow, heart, *etc.*) changes and adapts to the diseased liver.[1] These changes probably portend and prompt the final showdown in the patient's life, namely the acute decompensating event.[3] The microbiota, including bacteria (bacteriome), but also fungi (fungome) and viruses (virome), are also known to change during the development and progression of cirrhosis.[4] Several factors appear to affect the microbiota including the aetiology of liver disease, such as alcohol and diet (in the case of non-alcoholic fatty liver disease [NAFLD]).[5] CLD primarily reduces bile flow and causes cholestasis, which impairs the enterohepatic circulation and majorly affects the microbiota.[4,5] As CLD progresses, changes in microbiota (dysbiosis) are maintained and further exacerbated, probably by changes in intestinal motility, permeability, barrier function towards the lymphatic and blood compartment, portal hypertension and the immune system.[6] Yet the role of the microbiota seems to be pivotal in patients with decompensated cirrhosis, as many decompensating events are related to microbes or their interaction with the host.[7]

To describe the role of microbiota in cirrhosis and its role in decompensation, we first need to introduce acute decompensation (AD) and its most severe form acute-on-chronic liver failure (ACLF). AD defines the acute development of ascites, hepatic encephalopathy, gastrointestinal haemorrhage or bacterial infections, or any combination of these.[8] AD is a sudden and fast deterioration in health that is associated with dysfunction of the liver and extrahepatic organs, especially the kidneys and brain.[3] The most severe form of AD is

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Key points

Intestinal bacterial overgrowth and dysbiosis occur during progression of chronic liver disease and mutually drive and are aggravated by decompensation.

termed ACLF, which is associated with extremely high mortality approaching 40% at 28 days.[3,9]

Recently, the phenotype of patients with AD without ACLF, was characterised in the PREDICT study, which defined 3 separate groups of patients with AD: i) those with pre-ACLF, who present with high systemic inflammation, will develop ACLF in the following 90 days, and have very high mortality;[10] those with unstable decompensated cirrhosis, who will develop complications mainly due to severe portal hypertension (large ascites or bleeding requiring TIPS [transjugular intrahepatic portosystemic shunt]) and will be readmitted to the hospital <90 days after their index acute decompensation episode;[10] and the majority of patients with so-called stable decompensated cirrhosis. That said, 10% of patients with stable decompensated cirrhosis died within 1 year, having developed either ACLF or complications of portal hypertension. As highlighted above, different microbiota profiles may either benefit or exacerbate the liver phenotype and thereby precipitate decompensation and influence outcome in these patients. These effects support the rationale of targeting the microbiota using different tools (rifaximin, faecal microbiota transplantation [FMT]) to prevent and treat decompensation in cirrhosis. This is the topic of the current review, wherein we focus on the role of microbiota in the decompensation of patients with cirrhosis, as well as strategies targeting microbiota to prevent or treat decompensation.

Alteration of the microbiome and its associated changes in cirrhosis

The large observational prospective studies NACSELD, APASL-AARC, CANONIC and PREDICT identified several events deriving or possibly deriving from the gut microbiota or their products, which precipitate AD and ACLF.[9–14] Bacterial infection and alcoholic hepatitis are the precipitating events most commonly associated with acute decompensation, with recent data from the PREDICT study demonstrating that either of them (or their combination) account for 90% of identifiable precipitating events.[10] However, even in prospective, very detailed investigations, the precipitating event leading to acute decompensation cannot be determined in almost one-third of patients.[9,10] The microbiota and its metabolites may play a role in these undetermined cases, as shown recently.[14] The question that arises is, which changes in the microbiota during cirrhosis development and progression are relevant for the development of decompensation.

Changes in the microbiota occur early in the development of CLD, even before detectable liver damage, especially in alcohol-related CLD and NAFLD.[15] Different studies have shown shifts in the composition of the gut microbiome in different CLDs.[15,16] Yet, one common property of these changes, which is easy to assess, is the massive reduction in microbial diversity upon the development of cirrhosis and the even greater reduction upon decompensation.[17–19] In addition to reduced species diversity, bacterial overgrowth occurs in the small bowel, so-called small intestine bacterial overgrowth (SIBO),[20] which is partly due to decreased gut motility.[21] It is suspected that because of the sympathetic activation required to regulate the tone of dilated splanchnic vessels in cirrhosis, the motility of the gut is decreased, which leads to an increase in contact time of bacteria and thereby to fermentation changes in the luminal content.[22] This may lead to changes in the microbial metabolites, which may affect the epithelial cells and the liver itself. Specifically, formation of short-chain fatty acids (SCFAs) seems to be crucial in the homeostasis of the epithelial layer,[23] while different SCFAs may play a pathogenetic role in inflammation[24] and the liver disease itself.[25]

Despite SIBO and decreased richness, several studies have identified cirrhosis-specific profiles of the microbiota.[17,18,26,27] These profiles seem to be predominated by *Fusobacteria*, *Proteobacteria, Enterococcaceae* and *Streptococacceae* with relative decreases of *Bacteroidetes, Ruminococcus, Roseburia, Veillonellaceae* and *Lachnospiraceae* independent of cirrhosis aetiology.[17,18,26,27] The similarity of the microbiome changes in cirrhosis is quite important, since it demonstrates that the cirrhotic liver *per se* can impair the microbiota. This occurs when the aetiological agent has direct contact with the microbiome (alcohol-related or NASH-cirrhosis) and when the aetiology of the liver disease is not directly linked with the microbiome (hepatitis B and C). In addition to the increase in potential pathogenic taxa in cirrhosis, there is also a decrease in potential beneficial taxa, such as *Akkermansia* abundance, which was found to be decreased in patients with different liver disease aetiologies.[28–30] As mentioned, these profound changes in the microbiome are at least partly related to the liver disease itself rather than the direct effects of the aetiologic factor. This was confirmed by at least partial restoration of the gut microbiota after liver transplantation.[31]

Another reason for the dysbiotic composition of the cirrhotic microbiota is impaired enterohepatic circulation. Cirrhosis is associated with decreased secretion of primary bile acids into the gut lumen.[32] The secondary bile acids produced by bacteria are in turn decreased.[32–34] Moreover, bile acids are involved in the uptake of fat and fat-soluble proteins, and thereby have a tremendous influence on metabolism and possibly coagulation (Vitamin K-dependent coagulation factors) as well. Therefore, signs of malnutrition, including increased international normalised ratio, may be at least partly mediated by decreased primary and

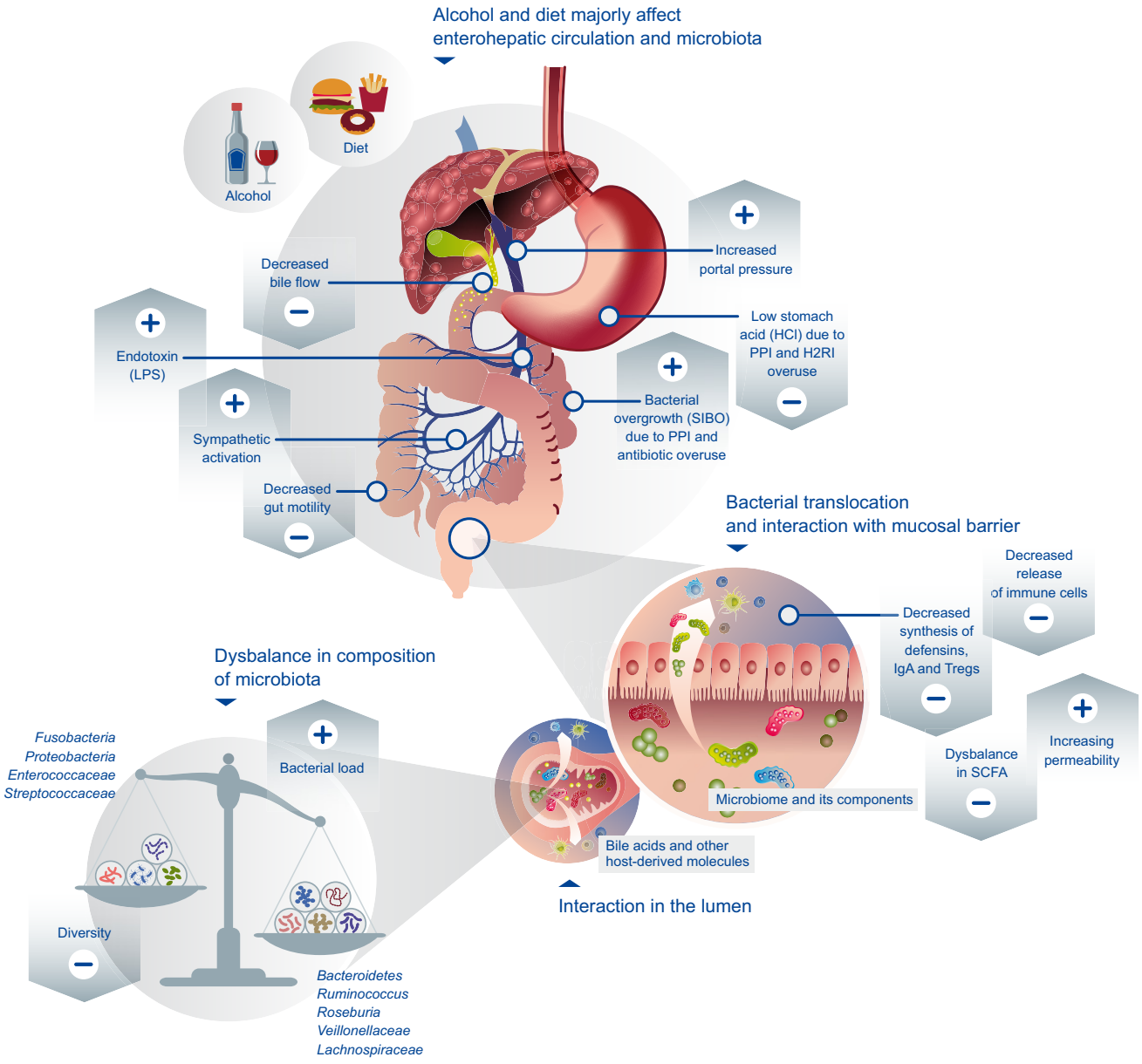

Fig. 1. Microbiome and decompensated cirrhosis. Changes during progression of cirrhosis affect to a large extent the microbiota. Especially alcohol and diet, decreased bile flow, portal hypertension and activation of sympathetic nervous system impair gut motility and permeability, lead to decreased diversity, but increased bacterial load and bacterial overgrowth, imbalance in bacterial species and finally increased bacterial translocation. SCFA, short-chain fatty acid.

secondary bile acid synthesis and uptake in cirrhosis. Bile acids are also strong modulators of the farnesoid X receptor (FXR)-axis, which is crucial in the homeostasis of the epithelial barrier and the gut-vascular barrier,[35,36] the impairment of which facilitates bacterial translocation. FXR has also been identified as a good target for treatment in cirrhosis, with decreased bacterial translocation following its agonism.[37,38] Bacterial translocation is also increased by structural changes to the intestinal epithelial layer, resulting from an increase in portal pressure (reviewed elsewhere[22]) and the changes in the type of resident and infiltrating immune cells.[38,39] The changes in the gut-associated immune system include decreased synthesis and release of antibacterial peptides, IgA, defensins and hypo- or achlorhydria.[40–42] Bacterial translocation, which is facilitated by the aforementioned changes to the microbiota and its functions, may then induce decompensation of cirrhosis (Fig. 1).

Microbiome changes and development of decompensation

Cirrhosis is associated with systemic inflammation as evidenced by increased systemic levels of oxidative stress, inflammatory cytokines, and markers of activated neutrophils and macrophages.[43–49] The degree

Key points

Acute decompensation, and especially its most severe forms, pre-ACLF and ACLF, are mainly precipitated by proven bacterial infection and/or severe alcoholic hepatitis, but also by bacterial translocation due to impaired intestinal barrier.

of systemic inflammation increases with liver disease severity, infections,[50] renal failure,[51] hepatic encephalopathy[52] and ACLF.[9] Gut-derived pathogen-associated molecular patterns are major inducers of systemic inflammation; they translocate through a disrupted gut barrier from the intestinal lumen via the portal vein to the liver and systemic circulation. Decompensation is characterised not only by worsening of this increased paracellular intestinal permeability, but also by translocation of viable bacteria. Bacteria likely translocate by transcytosis from the gut to the extraintestinal space and organs ,[53] where they cause infections (such as spontaneous bacterial peritonitis) and contribute to systemic inflammation, arterial vasodilation and organ failure.[43,54,55] Fungal infections in a cirrhotic inpatient cohort are associated with higher ACLF development rate and worse 30-day survival.[56]

Several mechanisms contribute to this additional layer of gut barrier dysfunction, which are all closely connected to intestinal dysbiosis. While intestinal bacterial overgrowth and changes in microbiota composition are common in patients with cirrhosis,[20] dysbiosis worsens during decompensation. Faecal microbial gene richness, microbial richness and species diversity are decreased in patients with decompensated cirrhosis compared with compensated cirrhosis.[57] A significant reduction in faecal Clostridiales XIV, Ruminococcaceae and Lachnospiraceae with a significant increase in pathogenic taxa such as Enterococcaceae, Staphylococcaceae and Enterobacteriaceae at the family level was found in patients with cirrhosis and worsening liver disease.[17] Using metagenomic sequencing, faecal *Alistipes indistinctus, Bilophila wadsworthia, Bilophila sp. 4_1_30, Ruminococcus champanellensis, Tannerella sp. 6_1_58FAA_CT1, Clostridium botulinum, Clostridium leptum, Clostridium methylpentosum* and *Clostridium sp. MSTE9* were lower, while *Veillonella atypica, Veillonella sp. ACP1*, *Veillonella dispar,* and *Veillonella sp.* oral taxon 158 were higher at the species level in patients with decompensated cirrhosis compared with compensated cirrhosis.[57] Changes in microbiota translate into functional metabolic differences.[57] Bacterial pathogenicity can be mediated via virulence factors. The toxin cytolysin, secreted by *Enterococcus faecalis* in the intestinal microbiota, associates with worse clinical outcomes and mortality in patients with alcoholic hepatitis.[58] While fungal dysbiosis and decreased fungal diversity is similar between patients with early stages of alcohol-associated liver disease and alcoholic hepatitis, the systemic immune response to fungal products is associated with increased mortality in patients with alcoholic hepatitis, likely because of impaired gut barrier function.[59] Candidalysin, a secreted exotoxin of *Candida albicans,* is associated with liver disease severity and mortality in patients with alcoholic hepatitis.[60] Cytolysin and candidalysin can directly damage primary hepatocytes, which might directly contribute to worsening liver function. Increased viral diversity was observed in faecal samples from patients with alcohol-associated liver disease, with the most significant changes in samples from patients with alcoholic hepatitis. Specific viral taxa, such as *Staphylococcus* phages and *Herpesviridae*, were associated with increased disease severity and 90-day mortality in patients with alcoholic hepatitis.[61] In a recent study of outpatients with cirrhosis, bacteriophages that differentially associated with bacteria over the course of disease were less likely than bacteria to predict 90-day hospitalisations. That said, phages focused on urease-producing *Streptococcus* were linked with the action of rifaximin in patients with cirrhosis and hepatic encephalopathy.[62] How changes in the intestinal virome contribute to hepatic decompensation is not known.

Dysbiosis causes intestinal inflammation, which in turn contributes to gut barrier dysfunction and pathological bacterial translocation.[63] Impaired antimicrobial activity in the intestine is associated with translocation of viable bacteria to the mesenteric lymph nodes in rats with cirrhosis and ascites.[42] Intestinal immune surveillance improves following intestinal decontamination with antibiotics in experimental cirrhosis, indicating that the bacterial microbiota contributes to exhausting the mucosal immune response during decompensation.[64]

Cholestasis causes a reflux of bile acids from the hepatocytes into the circulation and decreases bile flow into the biliary system and the intestine. Lower bile flow and less intestinal bile acids will further increase bacterial overgrowth and affect the composition of the gut microbiota during decompensation. Vice versa, dysbiosis changes intestinal bile acid metabolism and reduces the conversion of primary into secondary bile acids, which in turn can affect gut barrier function by modulating FXR activity.[38,65] Patients with advanced cirrhosis had the lowest total faecal bile acids, with a reduced ratio of secondary to primary bile acids compared to those with early cirrhosis and controls, while serum primary bile acids were higher in those with advanced cirrhosis than in those with early cirrhosis or controls.[32] Total and conjugated serum bile acids were shown to correlate positively with disease severity (model for end-stage liver disease [MELD]) in patients with alcoholic hepatitis.[66] In viral hepatitis, the mechanisms may be different. In these patients hepatic injury may lead to AD and ACLF via danger-associated molecular patterns.[67,68] Indeed, circulating bacterial DNA (a measure of bacterial translocation) was significantly increased in patients with HBV-related ACLF and correlated with inflammatory markers.[69]

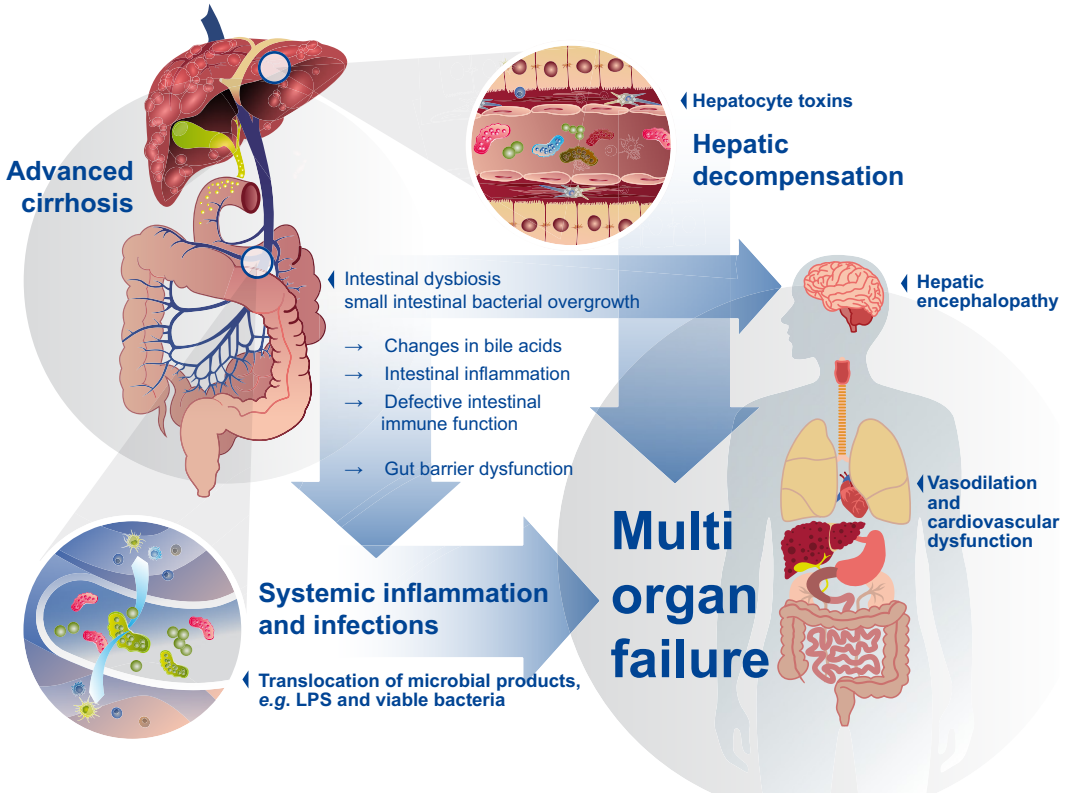

Fig. 2. Microbiome and hepatic decompensation. Worsening of liver disease initiates a cascade of events with intestinal bacterial overgrowth and dysbiosis as central events. Intestinal dysbiosis contributes to gut barrier function via several mechanisms. Increases in bacterial translocation lead to upregulation of systemic inflammation and infections, vasodilation and contribute to hepatic decompensation and multi-organ failure. Toxins produced by the microbiota can directly cause hepatocyte death and worsening of liver function.

Taken together, worsening liver disease initiates a cascade of events, of which intestinal bacterial overgrowth and dysbiosis are central. Bacterial toxins can directly cause hepatocyte death and worsening of liver function. Dysbiosis also affects gut barrier function and increases bacterial translocation, leading to infections, systemic inflammation and vasodilation, which contribute to acute decompensation and multi-organ failure. (Fig. 2).

Lactulose and nutrition as modulators of the gut microbiome

There are no published data employing untargeted or global culture-independent methodologies to assess the faecal microbiome in healthy individuals receiving lactulose. Lactulose has been shown to increase alpha diversity in healthy mice[70] and pigs,[71] as well as to increase Veillonellacaeae and Bifidobacteriaceae and to reduce Bacteroidaceae and Fusobacteriaceae in dogs.[72] The impact of lactulose in ameliorating dysbiosis in patients with cirrhosis is not clear cut. Studies utilising culture-dependent methodologies in patients with cirrhosis and minimal hepatic encephalopathy (HE) show increased *Bifidobacterium*, *Lactobacillus* and Bacteriodaceae colonies and reduced Enterobacteriaceae, *Enterococcus* and yeasts accompanying plasma ammonia reduction, improved psychometric tests and reduced risk of developing overt HE.[73] Furthermore, lactulose leads to a decreased faecal pH with increased aerobic and anaerobic bacterial counts and lactobacilli in patients with cirrhosis without HE.[74] Studies utilising 16S rDNA gene sequencing have failed to substantiate any impact of lactulose on the microbiome of patients with cirrhosis without HE and have reported only subtle changes in patients with HE,[75] including after lactulose withdrawal.[76]

The effects of dietary habits on clinical outcomes in patients with cirrhosis have been interrogated; for example, cirrhotic and control groups in the United States have been compared to groups from Turkey. The Turkish diet, rich in fermented milk products, coffee, tea, and chocolate, was associated with increased microbial diversity. Furthermore, it was shown that coffee, tea, vegetables, and cereals were protective against 90-day rehospitalisation rates.[77]

Potential therapeutic implications of new targets including

Faecal transplantation as a promising tool

The revolving door of hospitalisations, re-hospitalisations, antibiotic and proton pump

Key points

Bacteria and bacterial components are known to contribute to acute decompensation in cirrhosis both through direct hepatotoxicity and indirectly via increased systemic inflammation.

Table 1. Studies analysing FMT in cirrhosis.

Study and design	Samples/groups compared	Route and duration of FMT	Findings and significance	Limitations
Alcohol-related disorders				
Bajaj *et al.* Hepatology 2020 [147]	Men with AUD and cirrhosis who were not successful on abstinence using current therapies	• One-time enema *vs.* placebo • Reduced short-term alcohol craving and consumption with higher SCFA in FMT • Lower AUD-related hospitalisations long-term in FMT *vs.* placebo	Reduction of addictive behaviour resulting in long-term reduction in AUD-related hospitalisations over 6 months	• Small-scale • All men
Phillips *et al.* CGH 2017[148]	Men with steroid resistant alcohol-related hepatitis	• One week of daily NJT FMT from many donors • One year open-label study with historical controls	Higher survival *vs.* controls	• Open-label • Historical controls • All men
Phillips *et al.* Indian J Gastro 2018[149]	Men with alcohol-related hepatitis	• One week of daily NJT FMT from many donors *vs.* standard therapy • Three-month follow-up	3-month survival higher in FMT group, while 1-month survival was similar	• Open-label • Small numbers • All men
Cirrhosis				
Kao *et al.* Hepatol 2016[150]	One patient with HE	• 1 FMT via colonoscopy followed by 3 weekly enemas • Safe and well tolerated with improvement in cognitive function	Case report of FMT in cirrhosis with brain function improvement	• Case report
Bajaj *et al.* Hepatol 2017 and 2018[92,151]	20 HE patients on lactulose and rifaximin	• One 90 ml of enema after 5 days of broad-spectrum antibiotics • Safe and well tolerated, improvement in hospitalisations, dysbiosis and SCFAs post antibiotics after FMT	First randomised trial to study this in cirrhosis and HE and under Investigational new drug under FDA	• Small-scale • Antibiotics +FMT rather than FMT alone
Mehta *et al.* Indian J Gastro 2018[152] Case series	10 HE patients open-label	• One FMT via colonoscopy • Sustained clinical response at week 20 in 6 patients	Further evidence about safety and potential efficacy	• Open-label case series
Bajaj *et al.* Hepatology and JCI Insight 2019[93,153]	20 HE patients on lactulose and rifaximin	• 15 capsules of FMT *vs.* placebo once • Brain function improved and outcomes got better in those with secondary BA formation	Oral capsular FMT is also safe in HE and success can be linked to secondary BA formation.	• Small numbers

AUD, alcohol use disorder; BA, bile acid; FMT, faecal microbiota transplantation; HE, hepatic encephalopathy; NJT, nasojejunal tube; SCFA, short-chain fatty acid.

Table 2. Selected studies of rifaximin to reduce hepatic decompensation and improve outcomes.

Study and design	Samples/groups compared	Route and duration of therapy	Findings and significance	Limitations
Bass N *et al.* NEJM 2010;362(12):1071-81[108]	299 patients with cirrhosis with 2 or more overt HE episodes in the preceding 6-months.	Rifaximin 550 mg twice daily *vs.* placebo for 6 months. 91% of patients were on concomitant lactulose.	Rifaximin significantly reduced risk of HE, as compared with placebo, over a 6-month period (hazard ratio with rifaximin, 0.42; 95% CI 0.28–0.64; p <0.001). A breakthrough episode of HE occurred in 22.1% of patients on rifaximin, as compared with 45.9% of patients on placebo. 13.6% of the patients on rifaximin group had a hospitalisation involving HE, as compared with 22.6% of patients on placebo, hazard ratio of 0.50 (95% CI 0.29–0.87; p = 0.01).	MELD score 25 or less
Bajaj JS *et al.* PLoS One 2013;8(4):e60042[118]	20 patients with cirrhosis and minimal HE underwent cognitive testing, endotoxin analysis, urine/serum metabolomics and faecal microbiome assessment (16S rRNA) pre- and post-rifaximin.	Rifaximin 550 mg twice daily for 8-weeks	Rifaximin improved cognitive function and endotoxemia accompanied by alteration of gut bacterial linkages with metabolites without significant change in microbial abundance.	-
Orr JR *et al.* Liver Int. 2016;36(9):1295-303.[109]	326 patients in 10 UK centres.	Patients treated with rifaximin 550 mg twice daily. Data on hospital resource utilisation collected 12-months pre- and post-rifaximin therapy.	Initiation of treatment with rifaximin-α was associated with a marked reduction in the number of hospital admissions and hospital length of stay.	Retrospective study
Goel A *et al.* Aliment Pharmacol Ther. 2017; 46(11-12):1029-36.[112]	Five studies with 555 patients (295 rifaximin, 260 systemic antibiotics) compared rifaximin with systemic antibiotics.	Systematic review with meta-analysis: rifaximin for the prophylaxis of spontaneous bacterial peritonitis.	Rifaximin reduced the risk of SBP by 47% compared to no antibiotics for primary prophylaxis and by 74% compared to systemic antibiotics for secondary prophylaxis.	Systematic review with meta-analysis
Ibrahim ES *et al.* Eur J Gastroenterol Hepatol. 2017;29(11):1247-50[113]	80 patients with cirrhosis and ascites.	Randomised to rifaximin 550 mg twice daily for 12 weeks or standard of care.	Hepatorenal syndrome developed more in the control group than the rifaximin group [9 (22.5%) *vs.* 2 (5%); p = 0.048]	No placebo
Salehi S *et al.* Aliment Pharmacol Ther. 2019;50(4):435-41.[114]	622 patients listed for transplantation; 101 had HE	Outcomes of patients treated with rifaximin 550 mg twice daily *vs.* those who were naïve.	Patients on transplant waiting list treated with rifaximin had reduced all-cause admissions, episodes of spontaneous bacterial peritonitis and variceal bleeding. Multivariate regression analysis demonstrated that rifaximin was independently associated with an increase in average days to readmission (adjusted effect estimate 71, 95% CI 3-140 days).	Retrospective study

HE, hepatic encephalopathy; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis.

inhibitor (PPI) use, multiple instrumentations and inadequate dietary intake contribute to continued dysbiosis in cirrhosis.[78] Resetting this requires a major shift in the gut ecosystem through FMT. Studies in germ-free and specific-pathogen-free mice have shown that FMT from affected human donors can partly replicate microbial and brain-related injury even without continued exposure to the toxin(s) that caused the liver injury.[79–81] FMT has been extensively used to treat *Clostridium difficile* infections, which are characterised by an acute, major reduction in microbial diversity, unlike cirrhosis where there is a consistent gut-liver axis alteration. After FMT, bile acid moieties recover, indicating functional benefit.[82] Moreover, when exposed to liver injury, permissive microbiota were more likely to propagate liver damage[81] but FMT alone did not lead to cirrhosis.

The experience with FMT in humans with cirrhosis spans outpatients with compensated cirrhosis and alcohol use disorder (AUD), outpatients with HE on rifaximin and lactulose, and inpatients with alcoholic hepatitis[83] (Table 1). Moreover, it has been successfully used to treat concomitant *C. difficile*.[84–86] Several more studies are being planned or are in process to leverage this exciting approach.[87] Most current studies are small-scale, illustrating the first important step of any investigation, *i.e.* safety. Of note, there are no data for patients with complications (*e.g.* variceal bleeding) or decompensated patients. All studies demonstrate that this approach is safe even long-term and does not result in a greater incidence of infections if donors are screened according to guidelines.[88] When these protocols were not followed, donor-derived infections were easily transmitted to immunosuppressed patients.[88] Therefore, it is critical to select donors appropriately and in the era of COVID-19, ensuring that FMT is safe is even more important[89,90] (See Table 2).

As found in trials for *C. difficile*, FMT did not dramatically change the recipient's microbial composition or diversity.[91] Rather functional changes focused on bile acids, SCFAs and other metabolites were found.[92,93] Currently published trials are not powered for efficacy but nonetheless showed results that support the development and further refinement of FMT.

Hepatic encephalopathy: 1 case report, 1 case series and 2 small randomised controlled trials using enema, colonoscopy, and capsules have shown the safety of FMT. In studies that assessed cognition, FMT was shown to be associated with more frequent improvements than placebo/standard of care. Also, there were trends towards lower adverse events in the FMT compared to no-FMT group.

Alcohol use disorder: in a double-blind, placebo-controlled randomised clinical trial of men with AUD who had failed several attempts at pharmacological or behavioural therapy for abstinence, one-time enema FMT was safe over 6 months. There was a short-term reduction in alcohol craving and consumption accompanied by better microbial diversity and SCFA production in patients who underwent FMT. Over the long-term, AUD-related serious adverse events were significantly reduced in patients randomised to FMT (compared to placebo).

Alcohol-related hepatitis: the safety and potential benefit of FMT (compared to historical controls) was observed in steroid-ineligible patients over 1 year, while another open-label trial confirmed the safety of FMT.

The next steps are (a) defining efficacy (b) dose-response, (c) route of administration and (d) which microbe(s) are essential for potential beneficial impact. The risks and benefits of FMT must be balanced against the potential risks or absence of a viable therapeutic alternative. There should be an equipoise when employing FMT for cirrhosis. Given that the underlying liver aetiology also needs to be treated, it is important to continue efforts towards correcting the aetiology while pursuing FMT.

Key points

Targeting the microbiota may influence the rate of decompensation and thereby outcome in these patients.

Antibiotics in cirrhosis: A double-edged sword

Perturbations in the gut microbiome underpin the increased susceptibility of patients with cirrhosis to the development of infections, which may be asymptomatic in up to 50% of cases.[94] Bacterial translocation is a significant driver of cirrhosis-associated immune dysfunction, although the mechanisms by which intestinal dysbiosis drives immune cell dysfunction remain poorly characterised.[53,95] As infection is a potent precipitant of decompensating events, ACLF, and contributes to high mortality, patients are frequently prescribed broad-spectrum antibiotics.[96,97] Furthermore, approximately 25% of all patients with cirrhosis are on long-term antibiotics for the primary and secondary prophylaxis of spontaneous bacterial peritonitis (SBP)[98] and to prevent the recurrence of overt HE.[99] Whilst life-saving on the one hand, antibiotics are very much a double-edged sword, exacerbating pre-existing gut dysbiosis, augmenting disruption of the normally symbiotic population of intestinal bacteria and potentially predisposing to further opportunistic infections and SIBO.[100–102] This in turn adversely impacts on microbial diversity, composition, activity and gut wall integrity. Moreover, between 2011 and 2017/18, the prevalence of multidrug antimicrobial resistance (AMR) increased from 29% to 38% in culture-positive infections in patients with decompensated cirrhosis and ACLF.[97]

Manipulation of the gut microbiome in cirrhosis to reduce hepatic decompensation and improve outcomes

Rifaximin is an antibacterial drug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase

and consequently inhibits bacterial RNA synthesis. It has a broad antimicrobial spectrum against most gram-positive and negative, aerobic and anaerobic bacteria, including ammonia-producing species. It may inhibit the division of urea-deaminating bacteria, thereby reducing the production of ammonia and other compounds that play an important role in the pathogenesis of HE. Rifaximin can down-regulate microbe-induced gut epithelial inflammatory responses by inhibiting activation of NF-κB via the pregnane X receptor and by reducing the expression of the pro-inflammatory cytokines interleukin-1β and tumour necrosis factor-alpha (TNF-α).[103,104] Rifaximin also has eubiotic effects by selecting beneficial bacterial taxa.[105,106] Lactobacilli can grow in response to rifaximin administration, an effect restricted only to this antibiotic and not seen with another poorly absorbed antibiotic, neomycin.[107] Rifaximin reduces the risk of recurrence of overt HE and the need for hospitalisation; in conjunction with lactulose, it has become a mainstay second-line therapy for HE.[108] Rifaximin has been associated with significant reductions in hospitalisation, bed days, emergency department attendances and 30-day readmission.[109,110] The specific mechanism of action of rifaximin in HE remains to be elucidated and it has not been shown to appreciably lower blood ammonia levels in any study. As mentioned earlier, its action has been linked to bacteriophages that target urease-producing *Streptococcus*. Rifaximin reduces all-cause admissions, episodes of SBP and variceal bleeding, and length of hospitalisation in patients with advanced cirrhosis.[111–114] Furthermore, the use of rifaximin by patients on the liver transplant waiting list has been linked to reduced early allograft dysfunction following transplantation.[115] However, considerable concern remains regarding whether long-term rifaximin use may contribute to AMR in cirrhosis. Indeed, in a recent study, 50% of patients prescribed rifaximin for HE developed rifaximin-resistant staphylococcal isolates after as little as 1-7 weeks of rifaximin treatment.[116]

Antibiotics as modulators of inflammation in cirrhosis
Rifaximin reduces circulating levels of gut-derived endotoxins such as lipopolysaccharide.[117,118] Studies examining changes in the composition of the faecal microbiome in response to rifaximin have categorically failed to demonstrate any clear changes in microbial abundance by 16S rRNA faecal microbiota profiling.[118,119] However, a significant increase in serum saturated (myristic, caprylic, palmitic, palmitoleic, oleic and eicosanoic) and unsaturated (linoleic, linolenic, gamma-linolenic and arachnidonic) fatty acids post-rifaximin has been observed. Rifaximin led to a shift from pathogenic to beneficial metabolite linkages using network connectivity analysis centred on Enterobacteriaceae, Porphyromonadaceae and Bacteroidaceae.[118]

There are emerging data to suggest that rifaximin has potent anti-inflammatory actions including reducing anti-TNF-α and neutrophil toll-like receptor 4 expression.[120] Mucosal-associated invariant T (MAIT) cells are non-conventional T cells that display altered functions during chronic inflammatory diseases. MAIT cells are reduced in patients with alcoholic or NAFLD-related cirrhosis while they accumulate in liver fibrotic septa. In 2 models of chronic liver injury, MAIT cell-enriched mice show increased liver fibrosis and accumulation of hepatic fibrogenic cells, whereas MAIT cell-deficient mice were resistant to fibrosis. Long-term prophylactic antibiotic therapy with norfloxacin or rifaximin was significantly associated with a lower reduction in MAIT cell frequency.[121] Antibiotic-exposed patients with cirrhosis displayed significant reductions in CD25 expression, suggesting that long-term antibiotic therapy partially prevents MAIT cell reduction and activation .[121]

Adsorbents
Manipulation of the gut microbiome may also be achieved via adsorption of intraluminal host or microbial metabolites or ligands. Studies to date have focused on targeting enterosorption of pathogenic factors such as ammonia or endotoxin or modulation of bile acid pathways. The advantage of such an approach is that it does not confer a risk of AMR or introduce potential pathobionts. Conceptually the enterosorbants act as a 'sink' for pathological factors that would otherwise drive pathogenesis in liver disease.

Enterosorption of pathological bacterial ligands and metabolites
The first carbon-based enterosorbant to be evaluated in cirrhosis was AST-120 (Ocera Therapeutics Inc), a microporous carbon which had been demonstrated to efficiently adsorb ammonia *in vitro*. Bosoi *et al.* evaluated the capacity of AST-120 to lower blood ammonia, oxidative stress and brain oedema in bile duct ligated (BDL) rats, as both a prophylactic and therapeutic strategy.[122] Plasma ammonia concentrations in BDL rats were significantly decreased by AST-120 in a dose-dependent manner with normalisation of brain water content and locomotor activity. A multicentre, double-blind, randomised, placebo-controlled, dose-ranging study of AST-120 was conducted in patients with compensated cirrhosis, an MELD score ≤25 and covert hepatic encephalopathy (Astute study). AST-120 was found to be well tolerated but failed to achieve its primary endpoint of improvement in covert hepatic encephalopathy (Bajaj *et al.*, personal communication). A Cochrane review concluded that whilst AST-120 lowers blood ammonia concentrations

compared to placebo, there was little evidence this translated into clinical benefit.[123]

Yaq-001 (Yaqrit Limited, UK) is a more recent carbon-based enterosorbant that has been studied in cirrhosis. In contrast to AST-120, Yaq-001 is a non-absorbable synthetic carbon with a tailored bimodal distribution of porous domains within the macroporous range (>50 nm) and microporous range (<2 nm) and a very large surface area. The biological significance of this is that, in addition to binding smaller mediators such as indoles, acetaldehyde and fMLP, Yaq-001 exhibits rapid adsorption kinetics for larger molecular weight factors such as endotoxin, exotoxins and cytokines.[124] Yaq-001 was found to reduce liver injury, portal pressure and lipopolysaccharide-induced reactive oxygen species production in an *in vivo* model of cirrhosis and ACLF.[125] Whilst not exerting a direct effect on bacterial growth kinetics, shifts in microbiome composition were observed in stool.[126] Phase II clinical studies to evaluate safety, tolerability, and secondary efficacy endpoints have now been completed, with results due later this year.

Key points

Diet, lactulose, antibiotics (*e.g.* rifaximin), faecal microbial transplantation and enterosorbents (*e.g.* Yaq-001) are tools to prevent acute decompensation.

Modulation of bile acid pathways

Intraluminal bile acid availability exerts a selection pressure on microbiome composition. The gut microbiota has a reciprocal influence on the biotransformation of bile acids and downstream FXR and G protein-coupled membrane receptor 5 signalling pathways. Thus, manipulation of these pathways, using FXR agonists or by intraluminal sequestration of bile acids, represents a strategy to target the microbiome and impact on clinical outcomes.

The most well studied compound is the synthetic FXR agonist obeticholic acid (OCA), although many other therapeutic options have been developed, principally for pre-cirrhotic non-alcoholic steatohepatitis. An exhaustive discussion of these studies is beyond the scope of this review. In a rodent model of cirrhosis, OCA was found to significantly reduce bacterial translocation from 78.3% to 33.3% and significantly modulate mucosal microbiota composition.[38] Treatment was associated with favourable effects on ileal antimicrobial peptide, tight junction expression, intestinal inflammation and liver fibrosis. Clinical translation however has been hampered by safety concerns over OCA in patients with advanced disease.

Bile acid sequestration

The bile acid sequestrant colesevelam has been shown to attenuate cholestatic liver and bile duct injury in *Mdr2*$^{-/-}$ mice by modulating composition, signalling and excretion of faecal bile acids. Fuch *et al.* demonstrated that colesevelam increased faecal bile acid excretion and enhanced conversion to secondary bile acids, thereby attenuating liver and bile duct injury in *Mdr2*$^{-/-}$ mice.[127]

The phosphate sequestrant sevelamer has been studied in murine models of NASH because of its favourable effects on LDL cholesterol, attributed to sequestration of hydrophilic bile acids. Indeed, sevelamer was shown to prevent hepatic steatosis, inflammation and fibrosis.[128] Sevelamer improved a lower α-diversity and bound intraluminal endotoxin. Takahashi *et al.* demonstrated that in addition to demonstrating efficacy as a prophylactic strategy, sevelamer could reverse liver injury.[129] Metabolomic and microbiome analysis revealed that this beneficial effect is associated with changes in the microbiota population and bile acid composition, which are linked to improvements in insulin resistance.

Areas of controversy

There remain several areas of controversy in this burgeoning field, which can inform future trials.

The depth of coverage, functional assessment, metabolic activity and host response to microbiota vary between studies.[4] These factors, along with differing geographic areas, dietary practices, sex, ethnic variations, and aetiological differences can potentially alter the microbiome.[130,131] Therefore, these variables need to be controlled for in microbial analyses.

We do not know whether the microbiota is the "chicken or the egg" in human studies. In mice that have been humanised with stools from carefully phenotyped human donors, there is liver injury but not to the extent that is achieved by exposing the mice to the aetiological agent or to that found in the donor humans.[79,81,132] Therefore, the focus needs to be on determining the complicity of microbes at this stage.

An important source of controversy, is whether microbiota or their products mediate clinical outcomes.[14,32,58,60,133,134] There are redundancies in microbial function that can cross bacterial taxa and may be more relevant than composition. Studies isolating microbial products and/or dead bacteria offer a controversial insight into these differences.

Modern medical care has had a huge impact on the changes induced in the microbiome. The rampant overuse of antibiotics and PPIs can make the gut milieu in patients with cirrhosis hostile.[135,136] The controversy over routine use of antibiotic prophylaxis in patients with cirrhosis, especially in those who have not experienced SBP, is important from a clinical and microbiological perspective.[137] Antibiotics such as rifaximin may beneficially select taxa such as *Lactobacilli* which may protect against inflammation and hepatic decompensation[107,114] but others may promote hepatic toxicity. Further mechanistic studies are therefore warranted.

Furthermore, non-antibiotic drugs have a huge effect on the microbiome and may contribute to the development of antibiotic resistance, a growing

problem in this patient population.[138] Finally, we need to account for the impact of planned and also necessary endoscopic procedures, fasting periods and other interventions (*e.g.* professional periodontal cleaning) that may also induce at least temporary changes in the microbiome.[139,140] These factors may be crucial in the interpretation of cross-sectional microbiome research and require longitudinal large-scale and in-depth analysis with cautious interpretation that controls for these factors.

In addition, the role of non-bacterial microbiota such as fungi and viruses are important to elucidate since they interact with bacteria, with each other, and with their host in a complex ecosystem.[59–61,102] In selected circumstances they can become pathogenic. Virome constituents could potentially be used to treat specific infections or modulate the activity of target bacteria and their potential products.[58,141]

Microbial changes in easily accessible biofluids such as stool and saliva have been studied, but there are relatively few reports on microbiota from ascites, mucosal surfaces, liver tissue, bile and other tissues.[142–146] Microbial alterations in these tissues may be more closely linked to organ dysfunction. Therefore, the microbial milieu of these organs may be different and should not be conflated with stool or saliva unless there is further evidence.

Future perspectives

More detailed longitudinal, large-scale and in-depth analyses of the microbiota's role in liver disease are warranted. There remain several factors that can influence the microbiota, such as demographics (geographic area, sex and diet), aetiology, drugs, interventions, and finally the sampling compartment. These factors need to be controlled for and considered in the interpretation of future studies. Moreover, more mechanistic investigations on the role of the microbiota and its components are required to develop treatment strategies that can benefit patients without negatively influencing the gut ecosystem.

Current understanding on the composition and function of the gut microbiome and how this relates to progression and outcomes in patients with cirrhosis remains in its infancy and is based on descriptive snapshots afflicted with confounders and lacking robust clinical validation. As perturbations in the gut microbiome are a hallmark of advanced CLD that influence the rate of progression to liver failure and drive the susceptibility to infection, unlocking the potential of the microbiome and developing antibiotic-free therapies such as FMT to tackle these unmet needs is a research priority. Further multicentre randomised controlled trials are now needed to prove the efficacy of FMT in larger populations of patients with cirrhosis and to elucidate its mechanisms of action, which remain unclear.

Abbreviations

ACLF, acute-on-chronic liver failure; AD, acute decompensation; AUD, alcohol use disorder; BDL, bile duct ligated; CLD, chronic liver disease; FMT, faecal microbiota transplantation; FXR, farnesoid X receptor; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; SCFAs, short-chain fatty acids; SIBO, small intestine bacterial overgrowth.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

J.T. was responsible for drafting the chapters "Summary, Introduction, Alteration of the microbiome and its associated changes in cirrhosis, future perspectives", coordinating the writing and compiling the final version. J.M was responsible for drafting the chapter "Adsorbents". B.S. was responsible for drafting the chapters "Microbiome changes and development of decompensation, future perspectives" D.L.S. was responsible for

drafting the chapters “Antibiotics in cirrhosis: A double-edged sword, future perspectives” J.S.B. was responsible for drafting the chapters “Faecal transplantation as a promising tool, Area of controversy, future perspectives”. All authors revised and approved the manuscript.

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Supplementary data

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References

[1] Tsochatzis EA, Bosch J, Burroughs AK. Cirrhosis Lancet 2014;383:1749–1761.
[2] Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology 2008;134:1655–1669.
[3] Arroyo V, Moreau R, Jalan R. Acute-on-Chronic liver failure. N Engl J Med 2020;382:2137–2145.
[4] Tilg H, Cani PD, Mayer EA. Gut microbiome and liver diseases. Gut 2016;65:2035–2044.
[5] Tripathi A, Debelius J, Brenner DA, Karin M, Loomba R, Schnabl B, et al. The gut-liver axis and the intersection with the microbiome. Nat Rev Gastroenterol Hepatol 2018;15:397–411.
[6] Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: pathophysiological basis for therapy. J Hepatol 2020;72:558–577.
[7] Trebicka J, Reiberger T, Laleman W. Gut-liver Axis links portal hypertension to acute-on-chronic liver failure. Visc Med 2018;34:270–275.
[8] Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, et al. PREDICT identifies precipitating events associated with clinical course of acutely decompensated cirrhosis. J Hepatol 2020. accepted.
[9] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–1437. 1437 e1421-1429.
[10] Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, et al. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol 2020.
[11] Arroyo V, Moreau R, Kamath PS, Jalan R, Gines P, Nevens F, et al. Acute-on-chronic liver failure in cirrhosis. Nat Rev Dis Primers 2016;2:16041.
[12] Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. Nat Rev Gastroenterol Hepatol 2016;13:131–149.
[13] O'Leary JG, Reddy KR, Garcia-Tsao G, Biggins SW, Wong F, Fallon MB, et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology 2018;67:2367–2374.
[14] Bajaj JS, Reddy KR, O'Leary JG, Vargas HE, Lai JC, Kamath PS, et al. Serum levels of metabolites produced by intestinal microbes and lipid moieties independently associated with acute on chronic liver failure and death in patients with cirrhosis. Gastroenterology 2020.
[15] Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. Gastroenterology 2014;146:1513–1524.
[16] Bajaj JS. Alcohol, liver disease and the gut microbiota. Nat Rev Gastroenterol Hepatol 2019;16:235–246.
[17] Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014;60:940–947.
[18] Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, et al. Alterations of the human gut microbiome in cirrhosis. Nature 2014;513:59–64.
[19] Bajaj JS, Betrapally NS, Gillevet PM. Decompensated cirrhosis and microbiome interpretation. Nature 2015;525:E1–2.
[20] Bauer TM, Steinbruckner B, Brinkmann FE, Ditzen AK, Schwacha H, Aponte JJ, et al. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. Am J Gastroenterol 2001;96:2962–2967.
[21] Chang CS, Chen GH, Lien HC, Yeh HZ. Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis. Hepatology 1998;28:1187–1190.
[22] Fukui H, Wiest R. Changes of intestinal functions in liver cirrhosis. Inflamm Intest Dis 2016;1:24–40.
[23] Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. J Nutr 2009;139:1619–1625.
[24] Park J, Kim M, Kang SG, Jannasch AH, Cooper B, Patterson J, et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. Mucosal Immunol 2015;8:80–93.
[25] Chu H, Duan Y, Yang L, Schnabl B. Small metabolites, possible big changes: a microbiota-centered view of non-alcoholic fatty liver disease. Gut 2019;68:359–370.
[26] Chen Y, Yang F, Lu H, Wang B, Chen Y, Lei D, et al. Characterization of fecal microbial communities in patients with cirrhosis. Hepatology 2011;54:562–572.
[27] Oh TG, Kim SM, Caussy C, Fu T, Guo J, Bassirian S, et al. A universal gut-microbiome-derived signature predicts cirrhosis. Cell Metab 2020.
[28] Addolorato G, Ponziani FR, Dionisi T, Mosoni C, Vassallo GA, Sestito L, et al. Gut microbiota compositional and functional fingerprint in patients with alcohol use disorder and alcohol-associated liver disease. Liver Int 2020;40:878–888.
[29] Ponziani FR, Putignani L, Paroni Sterbini F, Petito V, Picca A, Del Chierico F, et al. Influence of hepatitis C virus eradication with direct-acting antivirals on the gut microbiota in patients with cirrhosis. Aliment Pharmacol Ther 2018;48:1301–1311.
[30] Ponziani FR, Bhoori S, Castelli C, Putignani L, Rivoltini L, Del Chierico F, et al. Hepatocellular carcinoma is associated with gut microbiota profile and inflammation in nonalcoholic fatty liver disease. Hepatology 2019;69:107–120.
[31] Bajaj JS, Fagan A, Sikaroodi M, White MB, Sterling RK, Gilles H, et al. Liver transplant modulates gut microbial dysbiosis and cognitive function in cirrhosis. Liver Transpl 2017;23:907–914.
[32] Kakiyama G, Pandak WM, Gillevet PM, Hylemon PB, Heuman DM, Daita K, et al. Modulation of the fecal bile acid profile by gut microbiota in cirrhosis. J Hepatol 2013;58:949–955.

[33] Ridlon JM, Alves JM, Hylemon PB, Bajaj JS. Cirrhosis, bile acids and gut microbiota: unraveling a complex relationship. Gut Microbes 2013;4:382–387.
[34] Kakiyama G, Hylemon PB, Zhou H, Pandak WM, Heuman DM, Kang DJ, et al. Colonic inflammation and secondary bile acids in alcoholic cirrhosis. Am J Physiol Gastrointest Liver Physiol 2014;306:G929–937.
[35] Wang YD, Chen WD, Moore DD, Huang W. FXR: a metabolic regulator and cell protector. Cell Res 2008;18:1087–1095.
[36] Sorribas M, Jakob MO, Yilmaz B, Li H, Stutz D, Noser Y, et al. FXR modulates the gut-vascular barrier by regulating the entry sites for bacterial translocation in experimental cirrhosis. J Hepatol 2019;71:1126–1140.
[37] Verbeke L, Farre R, Verbinnen B, Covens K, Vanuytsel T, Verhaegen J, et al. The FXR agonist obeticholic acid prevents gut barrier dysfunction and bacterial translocation in cholestatic rats. Am J Pathol 2015;185:409–419.
[38] Ubeda M, Lario M, Munoz L, Borrero MJ, Rodriguez-Serrano M, Sanchez-Diaz AM, et al. Obeticholic acid reduces bacterial translocation and inhibits intestinal inflammation in cirrhotic rats. J Hepatol 2016;64:1049–1057.
[39] Munoz L, Borrero MJ, Ubeda M, Conde E, Del Campo R, Rodriguez-Serrano M, et al. Intestinal immune dysregulation driven by dysbiosis promotes barrier disruption and bacterial translocation in rats with cirrhosis. Hepatology 2019;70:925–938.
[40] Shindo K, Machida M, Miyakawa K, Fukumura M. A syndrome of cirrhosis, achlorhydria, small intestinal bacterial overgrowth, and fat malabsorption. Am J Gastroenterol 1993;88:2084–2091.
[41] Pelletier G, Briantais MJ, Buffet C, Pillot J, Etienne JP. Serum and intestinal secretory IgA in alcoholic cirrhosis of the liver. Gut 1982;23:475–480.
[42] Teltschik Z, Wiest R, Beisner J, Nuding S, Hofmann C, Schoelmerich J, et al. Intestinal bacterial translocation in rats with cirrhosis is related to compromised Paneth cell antimicrobial host defense. Hepatology 2012;55:1154–1163.
[43] Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015;63:1272–1284.
[44] Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. Hepatology 2016;64:1249–1264.
[45] Sole C, Sola E, Morales-Ruiz M, Fernandez G, Huelin P, Graupera I, et al. Characterization of inflammatory response in acute-on-chronic liver failure and relationship with prognosis. Sci Rep 2016;6:32341.
[46] Gronbaek H, Rodgaard-Hansen S, Aagaard NK, Arroyo V, Moestrup SK, Garcia E, et al. Macrophage activation markers predict mortality in patients with cirrhosis without or with acute-on-chronic liver failure (ACLF). J Hepatol 2016;64:813–822.
[47] Trebicka J, Amoros A, Pitarch C, Titos E, Alcaraz-Quiles J, Schierwagen R, et al. Addressing profiles of systemic inflammation across the different clinical phenotypes of acutely decompensated cirrhosis. Front Immunol 2019;10:476.
[48] Monteiro S, Grandt J, Uschner FE, Kimer N, Madsen JL, Schierwagen R, et al. Differential inflammasome activation predisposes to acute-on-chronic liver failure in human and experimental cirrhosis with and without previous decompensation. Gut 2020.
[49] Praktiknjo M, Monteiro S, Grandt J, Kimer N, Madsen JL, Werge MP, et al. Cardiodynamic state is associated with systemic inflammation and fatal acute-on-chronic liver failure. Liver Int 2020;40:1457–1466.
[50] Michelena J, Altamirano J, Abraldes JG, Affo S, Morales-Ibanez O, Sancho-Bru P, et al. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. Hepatology 2015;62:762–772.
[51] Navasa M, Follo A, Filella X, Jimenez W, Francitorra A, Planas R, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. Hepatology 1998;27:1227–1232.
[52] Bajaj JS, Ridlon JM, Hylemon PB, Thacker LR, Heuman DM, Smith S, et al. Linkage of gut microbiome with cognition in hepatic encephalopathy. Am J Physiol Gastrointest Liver Physiol 2012;302:G168–175.
[53] Cirera I, Bauer TM, Navasa M, Vila J, Grande L, Taura P, et al. Bacterial translocation of enteric organisms in patients with cirrhosis. J Hepatol 2001;34:32–37.
[54] Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in cirrhosis. J Hepatol 2014;60:197–209.
[55] Frances R, Zapater P, Gonzalez-Navajas JM, Munoz C, Cano R, Moreu R, et al. Bacterial DNA in patients with cirrhosis and noninfected ascites mimics the soluble immune response established in patients with spontaneous bacterial peritonitis. Hepatology 2008;47:978–985.
[56] Bajaj JS, Reddy RK, Tandon P, Wong F, Kamath PS, Biggins SW, et al. Prediction of fungal infection development and their impact on survival using the NACSELD cohort. Am J Gastroenterol 2018;113:556–563.
[57] Shao L, Ling Z, Chen D, Liu Y, Yang F, Li L. Disorganized gut microbiome contributed to liver cirrhosis progression: a meta-omics-based study. Front Microbiol 2018;9:3166.
[58] Duan Y, Llorente C, Lang S, Brandl K, Chu H, Jiang L, et al. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. Nature 2019;575:505–511.
[59] Lang S, Duan Y, Liu J, Torralba MG, Kuelbs C, Ventura-Cots M, et al. Intestinal fungal dysbiosis and systemic immune response to fungi in patients with alcoholic hepatitis. Hepatology 2020;71:522–538.
[60] Chu H, Duan Y, Lang S, Jiang L, Wang Y, Llorente C, et al. The Candida albicans exotoxin candidalysin promotes alcohol-associated liver disease. J Hepatol 2020;72:391–400.
[61] Jiang L, Lang S, Duan Y, Zhang X, Gao B, Chopyk J, et al. Intestinal virome in patients with alcoholic hepatitis. Hepatology 2020.
[62] Bajaj J, Sikaroodi M, Shamsaddini A, Henseler Z, Santiago-Rodriguez T, Acharya C, et al. Interaction of bacterial metagenome and virome in patients with cirrhosis and hepatic encephalopathy. Gut 2020. in press.
[63] Chen P, Starkel P, Turner JR, Ho SB, Schnabl B. Dysbiosis-induced intestinal inflammation activates tumor necrosis factor receptor I and mediates alcoholic liver disease in mice. Hepatology 2015;61:883–894.
[64] Munoz L, Jose Borrero M, Ubeda M, Lario M, Diaz D, Frances R, et al. Interaction between intestinal dendritic cells and bacteria translocated from the gut in rats with cirrhosis. Hepatology 2012;56:1861–1869.
[65] Hartmann P, Hochrath K, Horvath A, Chen P, Seebauer CT, Llorente C, et al. Modulation of the intestinal bile acid/farnesoid X receptor/fibroblast growth factor 15 axis improves alcoholic liver disease in mice. Hepatology 2018;67:2150–2166.
[66] Brandl K, Hartmann P, Jih LJ, Pizzo DP, Argemi J, Ventura-Cots M, et al. Dysregulation of serum bile acids and FGF19 in alcoholic hepatitis. J Hepatol 2018;69:396–405.
[67] Shi Y, Yang Y, Hu Y, Wu W, Yang Q, Zheng M, et al. Acute-on-chronic liver failure precipitated by hepatic injury is distinct from that precipitated by extrahepatic insults. Hepatology 2015;62:232–242.
[68] Li H, Chen LY, Zhang NN, Li ST, Zeng B, Pavesi M, et al. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to hepatitis B. Sci Rep 2016;6:25487.
[69] Zhang Y, Zhao R, Shi D, Sun S, Ren H, Zhao H, et al. Characterization of the circulating microbiome in acute-on-chronic liver failure associated with hepatitis B. Liver Int 2019;39:1207–1216.
[70] Zhai S, Zhu L, Qin S, Li L. Effect of lactulose intervention on gut microbiota and short chain fatty acid composition of C57BL/6J mice. Microbiologyopen 2018;7:e00612.
[71] Chae JP, Pajarillo EA, Oh JK, Kim H, Kang DK. Revealing the combined effects of lactulose and probiotic enterococci on the swine faecal microbiota using 454 pyrosequencing. Microb Biotechnol 2016;9:486–495.
[72] Ferreira MDF, Salavati Schmitz S, Schoenebeck JJ, Clements DN, Campbell SM, Gaylor DE, et al. Lactulose drives a reversible reduction and qualitative modulation of the faecal microbiota diversity in healthy dogs. Sci Rep 2019;9:13350.
[73] Ziada DH, Soliman HH, El Yamany SA, Hamisa MF, Hasan AM. Can Lactobacillus acidophilus improve minimal hepatic encephalopathy? A neurometabolite study using magnetic resonance spectroscopy. Arab J Gastroenterol 2013;14:116–122.
[74] Riggio O, Varriale M, Testore GP, Di Rosa R, Di Rosa E, Merli M, et al. Effect of lactitol and lactulose administration on the fecal flora in cirrhotic patients. J Clin Gastroenterol 1990;12:433–436.
[75] Sarangi AN, Goel A, Singh A, Sasi A, Aggarwal R. Faecal bacterial microbiota in patients with cirrhosis and the effect of lactulose administration. BMC Gastroenterol 2017;17:125.
[76] Bajaj JS, Gillevet PM, Patel NR, Ahluwalia V, Ridlon JM, Kettenmann B, et al. A longitudinal systems biology analysis of lactulose withdrawal in hepatic encephalopathy. Metab Brain Dis 2012;27:205–215.
[77] Bajaj JS, Idilman R, Mabudian L, Hood M, Fagan A, Turan D, et al. Diet affects gut microbiota and modulates hospitalization risk differentially in an international cirrhosis cohort. Hepatology 2018;68:234–247.
[78] Bajaj JS, Vargas HE, Reddy KR, Lai JC, O'Leary JG, Tandon P, et al. Association between intestinal microbiota collected at hospital admission and outcomes of patients with cirrhosis. Clin Gastroenterol Hepatol 2019;17:756–765 e753.

[79] Kang DJ, Hylemon PB, Gillevet PM, Sartor RB, Betrapally NS, Kakiyama G, et al. Gut microbial composition can differentially regulate bile acid synthesis in humanized mice. Hepatol Commun 2017;1:61–70.
[80] Liu R, Kang JD, Sartor RB, Sikaroodi M, Fagan A, Gavis EA, et al. Neuroinflammation in murine cirrhosis is dependent on the gut microbiome and is attenuated by fecal transplant. Hepatology 2020;71:611–626.
[81] Llopis M, Cassard AM, Wrzosek L, Boschat L, Bruneau A, Ferrere G, et al. Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease. Gut 2016;65:830–839.
[82] Weingarden A, Gonzalez A, Vazquez-Baeza Y, Weiss S, Humphry G, Berg-Lyons D, et al. Dynamic changes in short- and long-term bacterial composition following fecal microbiota transplantation for recurrent Clostridium difficile infection. Microbiome 2015;3:10.
[83] Bajaj JS, Khoruts A. Microbiota changes and intestinal microbiota transplantation in liver diseases and cirrhosis. J Hepatol 2020;72:1003–1027.
[84] Pringle PL, Soto MT, Chung RT, Hohmann E. Patients with cirrhosis require more fecal microbiota capsules to cure refractory and recurrent Clostridium difficile infections. Clin Gastroenterol Hepatol 2019;17:791–793.
[85] Meighani A, Alimirah M, Ramesh M, Salgia R. Fecal microbiota transplantation for clostridioides difficile infection in patients with chronic liver disease. Int J Hepatol 2020;2020:1874570.
[86] Cheng YW, Alhaffar D, Saha S, Khanna S, Bohm M, Phelps E, et al. Fecal microbiota transplantation is safe and effective in patients with clostridioides difficile infection and cirrhosis. Clin Gastroenterol Hepatol 2020.
[87] Hatton GB, Ran S, Tranah TH, Shawcross DL. Lessons learned from faecal microbiota transplantation in cirrhosis. Curr Hepatol Rep 2020.
[88] DeFilipp Z, Bloom PP, Torres Soto M, Mansour MK, Sater MRA, Huntley MH, et al. Drug-resistant E. coli bacteremia transmitted by fecal microbiota transplant. N Engl J Med 2019;381:2043–2050.
[89] Ianiro G, Mullish BH, Kelly CR, Kassam Z, Kuijper EJ, Ng SC, et al. Reorganisation of faecal microbiota transplant services during the COVID-19 pandemic. Gut 2020;69:1555–1563.
[90] Kassam Z, Dubois N, Ramakrishna B, Ling K, Qazi T, Smith M, et al. Donor screening for fecal microbiota transplantation. N Engl J Med 2019;381:2070–2072.
[91] Weingarden AR, Chen C, Bobr A, Yao D, Lu Y, Nelson VM, et al. Microbiota transplantation restores normal fecal bile acid composition in recurrent Clostridium difficile infection. Am J Physiol Gastrointest Liver Physiol 2014;306:G310–319.
[92] Bajaj JS, Kakiyama G, Savidge T, Takei H, Kassam ZA, Fagan A, et al. Antibiotic-associated disruption of microbiota composition and function in cirrhosis is restored by fecal transplant. Hepatology 2018;68:1549–1558.
[93] Bajaj JS, Salzman NH, Acharya C, Sterling RK, White MB, Gavis EA, et al. Fecal microbial transplant capsules are safe in hepatic encephalopathy: a phase 1, randomized, placebo-controlled trial. Hepatology 2019;70:1690–1703.
[94] Borzio M, Salerno F, Piantoni L, Cazzaniga M, Angeli P, Bissoli F, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. Dig Liver Dis 2001;33:41–48.
[95] Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014;61:1385–1396.
[96] Fernandez J, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018;67:1870–1880.
[97] Fernandez J, Prado V, Trebicka J, Amoros A, Gustot T, Wiest R, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol 2019;70:398–411.
[98] European Association for the Study of the Liver. Electronic address eee, clinical practice guideline panel C, panel m, representative EGB. EASL clinical practice guidelines: drug-induced liver injury. J Hepatol 2019;70:1222–1261.
[99] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American association for the study of liver diseases and the European association for the study of the liver. Hepatology 2014;60:715–735.
[100] Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014;60:940–947.
[101] Francino MP. Antibiotics and the human gut microbiome: dysbiosesand accumulation of resistances. Front Microbiol 2016;6.
[102] Bajaj JS, Liu EJ, Kheradman R, Fagan A, Heuman DM, White M, et al. Fungal dysbiosis in cirrhosis. Gut 2018;67:1146–1154.
[103] Hirota SA. Understanding the molecular mechanisms of rifaximin in the treatment of gastrointestinal disorders–A focus on the modulation of host tissue function. Mini Rev Med Chem 2015;16:206–217.
[104] Mencarelli A, Migliorati M, Barbanti M, Cipriani S, Palladino G, Distrutti E, et al. Pregnane-X-receptor mediates the anti-inflammatory activities of rifaximin on detoxification pathways in intestinal epithelial cells. Biochem Pharmacol 2010;80:1700–1707.
[105] 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.
[106] Ponziani FR, Zocco MA, D'Aversa F, Pompili M, Gasbarrini A. Eubiotic properties of rifaximin: disruption of the traditional concepts in gut microbiota modulation. World J Gastroenterol 2017;23:4491–4499.
[107] Xu D, Gao J, Gillilland 3rd M, Wu X, Song I, Kao JY, et al. Rifaximin alters intestinal bacteria and prevents stress-induced gut inflammation and visceral hyperalgesia in rats. Gastroenterology 2014;146:484–496 e484.
[108] Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362:1071–1081.
[109] Orr JG, Currie CJ, Berni E, Goel A, Moriarty KJ, Sinha A, et al. The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin-alpha. Liver Int 2016;36:1295–1303.
[110] Hudson M, Radwan A, Di Maggio P, Cipelli R, Ryder SD, Dillon JF, et al. The impact of rifaximin-alpha on the hospital resource use associated with the management of patients with hepatic encephalopathy: a retrospective observational study (IMPRESS). Frontline Gastroenterol 2017;8:243–251.
[111] Kang DJ, Kakiyama G, Betrapally NS, Herzog J, Nittono H, Hylemon PB, et al. Rifaximin exerts beneficial effects independent of its ability to alter microbiota composition. Clin Transl Gastroenterol 2016;7:e187.
[112] Goel A, Rahim U, Nguyen LH, Stave C, Nguyen MH. Systematic review with meta-analysis: rifaximin for the prophylaxis of spontaneous bacterial peritonitis. Aliment Pharmacol Ther 2017;46:1029–1036.
[113] Ibrahim ES, Alsebaey A, Zaghla H, Moawad Abdelmageed S, Gameel K, Abdelsameea E. Long-term rifaximin therapy as a primary prevention of hepatorenal syndrome. Eur J Gastroenterol Hepatol 2017;29:1247–1250.
[114] Salehi S, Tranah TH, Lim S, Heaton N, Heneghan M, Aluvihare V, et al. Rifaximin reduces the incidence of spontaneous bacterial peritonitis, variceal bleeding and all-cause admissions in patients on the liver transplant waiting list. Aliment Pharmacol Ther 2019;50:435–441.
[115] Ito T, Nakamura K, Kageyama S, Korayem IM, Hirao H, Kadono K, et al. Impact of rifaximin therapy on ischemia/reperfusion injury in liver transplantation: a propensity score-matched analysis. Liver Transpl 2019;25:1778–1789.
[116] Chang JY, Kim SE, Kim TH, Woo SY, Ryu MS, Joo YH, et al. Emergence of rifampin-resistant staphylococci after rifaximin administration in cirrhotic patients. PLoS One 2017;12:e0186120.
[117] Kalambokis GN, Tsianos EV. Rifaximin reduces endotoxemia and improves liver function and disease severity in patients with decompensated cirrhosis. Hepatology 2012;55:655–656.
[118] Bajaj JS, Heuman DM, Sanyal AJ, Hylemon PB, Sterling RK, Stravitz RT, et al. Modulation of the metabiome by rifaximin in patients with cirrhosis and minimal hepatic encephalopathy. PLoS One 2013;8:e60042.
[119] Kimer N, Pedersen JS, Tavenier J, Christensen JE, Busk TM, Hobolth L, et al. Rifaximin has minor effects on bacterial composition, inflammation, and bacterial translocation in cirrhosis: a randomized trial. J Gastroenterol Hepatol 2018;33:307–314.
[120] Zeng X, Tang XJ, Sheng X, Ni W, Xin HG, Chen WZ, et al. Does low-dose rifaximin ameliorate endotoxemia in patients with cirrhosis: a prospective study. J Dig Dis 2015;16:665–674.
[121] Hegde P, Weiss E, Paradis V, Wan J, Mabire M, Sukriti S, et al. Mucosal-associated invariant T cells are a profibrogenic immune cell population in the liver. Nat Commun 2018;9:2146.
[122] Bosoi CR, Parent-Robitaille C, Anderson K, Tremblay M, Rose CF. AST-120 (spherical carbon adsorbent) lowers ammonia levels and attenuates brain edema in bile duct-ligated rats. Hepatology 2011;53:1995–2002.
[123] Zacharias HD, Zacharias AP, Gluud LL, Morgan MY. Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis. Cochrane Database Syst Rev 2019;6:CD012334.

[124] Tripisciano C, Kozynchenko OP, Linsberger I, Phillips GJ, Howell CA, Sandeman SR, et al. Activation-dependent adsorption of cytokines and toxins related to liver failure to carbon beads. Biomacromolecules 2011;12:3733–3740.
[125] De Chiara F, Li J, Lu W, Davies N, Mookerjee RP, Jalan R, et al. Characterization of the protective effects of Yaq-001 on organ injury in cirrhosis. J Hepatol 2018;68:S463.
[126] Macnaughtan J, Ranchal I, Soeda J, Sawhney R, Oben J, Davies N, et al. Oral therapy with non-absorbable carbons of controlled porosity (Yaq-001) selectively modulates stool microbiome and its function and this is associated with restoration of immune function and inflammasome activation. J Hepatol 2015;62. S240-S240.
[127] Fuchs CD, Paumgartner G, Mlitz V, Kunczer V, Halilbasic E, Leditznig N, et al. Colesevelam attenuates cholestatic liver and bile duct injury in Mdr2(-/-) mice by modulating composition, signalling and excretion of faecal bile acids. Gut 2018;67:1683–1691.
[128] Tsuji Y, Kaji K, Kitade M, Kaya D, Kitagawa K, Ozutsumi T, et al. Bile acid sequestrant, sevelamer ameliorates hepatic fibrosis with reduced overload of endogenous lipopolysaccharide in experimental nonalcoholic steatohepatitis. Microorganisms 2020;8.
[129] Takahashi S, Luo Y, Ranjit S, Xie C, Libby AE, Orlicky DJ, et al. Bile acid sequestration reverses liver injury and prevents progression of nonalcoholic steatohepatitis in Western diet-fed mice. J Biol Chem 2020;295:4733–4747.
[130] Johnson AJ, Zheng JJ, Kang JW, Saboe A, Knights D, Zivkovic AM. A guide to diet-microbiome study design. Front Nutr 2020;7:79.
[131] Saboo K, Shamsaddini A, Iyer MV, Hu C, Fagan A, Gavis EA, et al. Sex is associated with differences in gut microbial composition and function in hepatic encephalopathy. J Hepatol 2020.
[132] Mazagova M, Wang L, Anfora AT, Wissmueller M, Lesley SA, Miyamoto Y, et al. Commensal microbiota is hepatoprotective and prevents liver fibrosis in mice. FASEB J 2015;29:1043–1055.
[133] Levy M, Thaiss CA, Elinav E. Metabolites: messengers between the microbiota and the immune system. Genes Dev 2016;30:1589–1597.
[134] Hartmann P, Hochrath K, Horvath A, Chen P, Seebauer CT, Llorente C, et al. Modulation of the intestinal bile acid-FXR-FGF15 axis improves alcoholic liver disease in mice. Hepatology 2017.
[135] Horvath A, Rainer F, Bashir M, Leber B, Schmerboeck B, Klymiuk I, et al. Biomarkers for oralization during long-term proton pump inhibitor therapy predict survival in cirrhosis. Sci Rep 2019;9:12000.
[136] Bajaj JS, Acharya C, Fagan A, White MB, Gavis E, Heuman DM, et al. Proton pump inhibitor initiation and withdrawal affects gut microbiota and readmission risk in cirrhosis. Am J Gastroenterol 2018;113:1177–1186.
[137] Fernandez J, Tandon P, Mensa J, Garcia-Tsao G. Antibiotic prophylaxis in cirrhosis: good and bad. Hepatology 2016;63:2019–2031.
[138] Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature 2018;555:623–628.
[139] Liu Z, Dai X, Zhang H, Shi R, Hui Y, Jin X, et al. Gut microbiota mediates intermittent-fasting alleviation of diabetes-induced cognitive impairment. Nat Commun 2020;11:855.
[140] Bajaj JS, Matin P, White MB, Fagan A, Deeb JG, Acharya C, et al. Periodontal therapy favorably modulates the oral-gut-hepatic axis in cirrhosis. Am J Physiol Gastrointest Liver Physiol 2018;315:G824–G837.
[141] Abedon ST, Thomas-Abedon C. Phage therapy pharmacology. Curr Pharm Biotechnol 2010;11:28–47.
[142] Bajaj JS, Betrapally NS, Hylemon PB, Heuman DM, Daita K, White MB, et al. Salivary microbiota reflects changes in gut microbiota in cirrhosis with hepatic encephalopathy. Hepatology 2015;62:1260–1271.
[143] 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.
[144] Santiago A, Pozuelo M, Poca M, Gely C, Nieto JC, Torras X, et al. Alteration of the serum microbiome composition in cirrhotic patients with ascites. Sci Rep 2016;6:25001.
[145] Schierwagen R, Alvarez-Silva C, Madsen MSA, Kolbe CC, Meyer C, Thomas D, et al. Circulating microbiome in blood of different circulatory compartments. Gut 2019;68:578–580.
[146] Ye F, Shen H, Li Z, Meng F, Li L, Yang J, et al. Influence of the biliary system on biliary bacteria revealed by bacterial communities of the human biliary and upper digestive tracts. PLoS One 2016;11:e0150519.
[147] Bajaj JS, Gavis EA, Fagan A, Wade JB, Thacker LR, Fuchs M, et al. A randomized clinical trial of fecal microbiota transplant for alcohol use disorder. Hepatology 2020.
[148] Philips CA, Pande A, Shasthry SM, Jamwal KD, Khillan V, Chandel SS, et al. Healthy donor fecal microbiota transplantation in steroid-ineligible severe alcoholic hepatitis: a pilot study. Clin Gastroenterol Hepatol 2017;15:600–602.
[149] Philips CA, Phadke N, Ganesan K, Ranade S, Augustine P. Corticosteroids, nutrition, pentoxifylline, or fecal microbiota transplantation for severe alcoholic hepatitis. Indian J Gastroenterol 2018;37:215–225.
[150] Kao D, Roach B, Park H, Hotte N, Madsen K, Bain V, et al. Fecal microbiota transplantation in the management of hepatic encephalopathy. Hepatology 2016;63:339–340.
[151] Bajaj JS, Kassam Z, Fagan A, Gavis EA, Liu E, Cox IJ, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. Hepatology 2017;66:1727–1738.
[152] Mehta R, Kabrawala M, Nandwani S, Kalra P, Patel C, Desai P, et al. Preliminary experience with single fecal microbiota transplant for treatment of recurrent overt hepatic encephalopathy-A case series. Indian J Gastroenterol 2018;37:559–562.
[153] Bajaj JS, Salzman N, Acharya C, Takei H, Kakiyama G, Fagan A, et al. Microbial functional change is linked with clinical outcomes after capsular fecal transplant in cirrhosis. JCI Insight 2019;4.