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## Clinical impact of microbiome in patients with decompensated cirrhosis

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### Abstract

Cirrhosis is an increasing cause of morbidity and mortality. Recent studies are trying to clarify the role of microbiome in clinical exacerbation of patients with decompensated cirrhosis. Nowadays, it is accepted that patients with cirrhosis have altered salivary and enteric microbiome, characterized by the presence of dysbiosis. This altered microbiome along with small bowel bacterial overgrowth, through translocation across the gut, is associated with the development of decompensating complications. Studies have analyzed the correlation of certain bacterial families with the development of hepatic encephalopathy in cirrhotics. In general, stool and saliva dysbiosis with reduction of autochthonous bacteria in patients with cirrhosis incites changes in bacterial defenses and higher risk for bacterial infections, such as spontaneous bacterial peritonitis, and sepsis. Gut microbiome has even been associated with oncogenic pathways and under circumstances might promote the development of hepatocarcinogenesis. Lately, the existence of the oral-gut-liver axis has been related with the development of decompensating events. This link between the liver and the oral cavity could be *via* the gut through impaired intestinal permeability that allows direct translocation of bacteria from the oral cavity to the systemic circulation. Overall, the contribution of the microbiome to pathogenesis becomes more pronounced with progressive disease and therefore may represent an important therapeutic



target in the management of cirrhosis.

**Key words:** Microbiome; Dysbiosis; Oral-gut-liver axis; Hepatic encephalopathy; Decompensated cirrhosis; Liver carcinoma

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**Core tip:** Human microbiome of the oral-gut-liver axis is implicated in the progression of hepatic diseases and the development of decompensated events. Its significance over diagnostic, prognostic and therapeutic possibilities drives a new era in the management of patients with cirrhosis.

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## INTRODUCTION

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries, being the 14<sup>th</sup> most common cause of death worldwide<sup>[1]</sup>. Decompensated disease has an annual mortality rate of 57%, and acute decompensating events present mortality of 30%<sup>[1]</sup>. Traditionally, clinicians use models to triage patients with advanced liver diseases; Model for End stage Liver Disease (MELD) and Child-Pugh (CTP) scores have been validated and provide significant prognostic information<sup>[2,3]</sup>.

In the era of advanced molecular techniques, human microbiome is being studied for the pathogenesis and superior prognostication of decompensated patients<sup>[4]</sup>. The microbial imbalance or dysbiosis that occurs in the gut in patients with cirrhosis has recently been linked with complications of cirrhosis, including hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), and sepsis<sup>[5]</sup>.

At least for the last decade, it is known that the gut flora contributes in the pathogenesis of cirrhosis' complications, regarding the development of infections or the hyperdynamic circulatory state of cirrhosis<sup>[6]</sup>. Here, we reviewed data regarding the role of microbiome in clinical exacerbation of patients with decompensated cirrhosis.

## HUMAN MICROBIOME

Human microbiome stands the community of bacteria, archaea, fungi, and viruses which are found and interact within a body habitat, such as oral cavity or gut<sup>[7]</sup>. It is characterized by its diversity and microbial abundance

and performs specific metabolic and functional pathways<sup>[8]</sup>. Using culture-independent techniques, which analyze the DNA extracted directly from a sample, allow us to investigate several aspects of microbial communities, their causative or modulatory roles<sup>[7]</sup>. The challenge in microbiome analysis concerns the relation between differences in community composition to differences in function, therefore identify the human microbiome as a biomarker for specific clinical conditions<sup>[9]</sup>.

## ALTERED MICROBIOME IN PATIENTS WITH CIRRHOSIS

A few studies tried to map the human microbiome of patients with advanced liver diseases. Data regarding decompensated cirrhotic patients are far more scarce. A first comprehensive view into the intestinal microbiome of patients with cirrhosis showed that the fecal microbial composition of patients with cirrhosis is distinct from healthy controls. Patients presented with prevalence of potentially pathogenic bacteria, such as *Enterobacteriaceae*, *Veillonellaceae* and *Streptococcaceae*, which had a positive correlation with CTP score. Proteobacteria and Fusobacteria were highly enriched along with the reduction of beneficial populations such as *Lachnospiraceae* which correlated negatively with CTP score<sup>[10]</sup>. A next analysis of stool microbiome conducted in cirrhotics showed that the composition differed significantly<sup>[11]</sup>.

Bajaj *et al*<sup>[12]</sup> studied 54 decompensated cirrhotic patients and proposed the cirrhosis dysbiosis ratio (CDR), ratio of autochthonous to non-autochthonous taxa, as a tool to estimate dysbiosis in cirrhotics. Microbiota and CDR were relatively stable over time within patients whose disease remained unchanged and altered when the underlying disease worsened. CDR for controls was significantly higher compared to all cirrhotic patients.

In 2014 Qin *et al*<sup>[13]</sup> analyzed data regarding the gut microbiome of patients with cirrhosis and reported two principal findings; patients with cirrhosis had altered gut microbiome profile compared to healthy controls, and most (54%) of the patient-enriched species were of buccal origin, suggesting a massive invasion of the gut by oral bacterial species from the mouth, responsible for this change of the gut microbiota seen in cirrhosis. These findings established new perspectives over the role of oral-gut-liver axis in patients with cirrhosis.

Accordingly, a further evaluation of the salivary and stool microbiome in decompensated cirrhotic patients showed dysbiosis represented by reduction in autochthonous bacteria, both in saliva and stool samples<sup>[14]</sup>. This was related to impaired salivary defenses and worse salivary and systemic inflammation, more prominent in patients with HE. Patients with cirrhosis had a significantly lower relative abundance of autochthonous taxa (*Lachnospiraceae*, *Ruminococcaceae*, and *Clostridiales* XIV) and significantly lower stool cirrhosis dysbiosis ratio

(*Lachnospiraceae* + *Ruminococcaceae* + *Clostridiales Incertae Sedis* XIV + *Veillonellaceae/Enterobacteriaceae* + *Bacteroidaceae*) and salivary microbiota dysbiosis ratio (*Lachnospiraceae* + *Ruminococcaceae* + *Clostridiales Incertae Sedis* XIV/*Streptococcaceae*)<sup>[14]</sup>. Chen *et al.*<sup>[15]</sup>, showed that even the duodenal mucosa microbiota in cirrhotic patients is dramatically different from healthy controls, possibly in accordance with alterations of oral microbiota and changes in duodenal micro-environment. *Veillonella*, *Prevotella*, *Neisseria*, and *Haemophilus*, found to be the most discriminative taxa between cirrhosis and controls.

Dysbiosis of the oral microbiota was present in patients with chronic liver disease; *i.e.*, chronic hepatitis B and hepatitis B related cirrhosis. One correspondent study supported that the higher proportion of *Firmicutes* than of *Bacteroidetes* organisms is responsible for the weak oral defenses that contributes to the breakdown of oral defenses and invasion of the gut. So, dysbiosis was introduced as inversion of the *Firmicutes/Bacteroidetes* ratio<sup>[16]</sup>. Lately, oral microbiome was characterized by significant dysbiosis in cirrhotic patients with hepatocellular carcinoma (HCC), suggesting that certain key bacterial species may characterize patients' microbiota<sup>[17]</sup>. Overall, these findings suggest new potential prognostic and therapeutic targets.

## **PATHOPHYSIOLOGY: THE ROLE OF MICROBIOME OVER THE ORAL-GUT-LIVER AXIS**

Published research findings reveal implications of the altered microbiome in the progress of liver diseases. The microbiome determines likelihood and rate of progression of liver injury, complications of cirrhosis and ultimately outcome<sup>[18]</sup>. The principal theory highlights the role of the gut-liver axis in the development and progression of cirrhosis and portal hypertension; bacterial translocation (BT) from the intestine reaches the liver and increases portal pressure, while, on the other hand, portal hypertension leads to intestinal edema, disruption of epithelial integrity and more translocation<sup>[19]</sup>.

The microbiome has been considered the "core facility" for the production of a myriade of bacterial metabolites and products to which the gut-vascular barrier and each member of the gut-liver-axis are exposed<sup>[20]</sup>. Cirrhotic patients are exposed to a higher risk of dysbiosis because of a variety of pathological interactions between the liver and the gastrointestinal tract. Alteration in intestinal motility, higher gastric pH and reduced bile acid concentration in the colon, may lead to a failure in the control of bacterial intestinal growth<sup>[21]</sup>. During progression of cirrhosis, the microbiome, through their metabolism, cell wall components (LPS) and translocation, leads to inflammation. Inflammation suppresses synthesis of bile acids in liver supporting a positive-feedback mechanism. Decrease in bile acids entering the intestines appears to favor overgrowth

of pathogenic and pro-inflammatory members of the microbiome<sup>[22]</sup>. Moreover, dysbiosis seems to co-exist with small intestinal bacterial overgrowth (SIBO) related to delayed intestinal transit and the development of cirrhotic complications<sup>[23]</sup>. Overall, intestinal dysbiosis is established in decompensated liver disease. This was found to represent a condition of reduced relative abundance of taxa considered benign and autochthonous, including *Lachnospiraceae*, *Ruminococcaceae*, and *Clostridiales Incertae Sedis* XIV and a relatively higher abundance of others, particularly *Enterobacteriaceae* and *Bacteroidaceae*<sup>[12,14,16]</sup>.

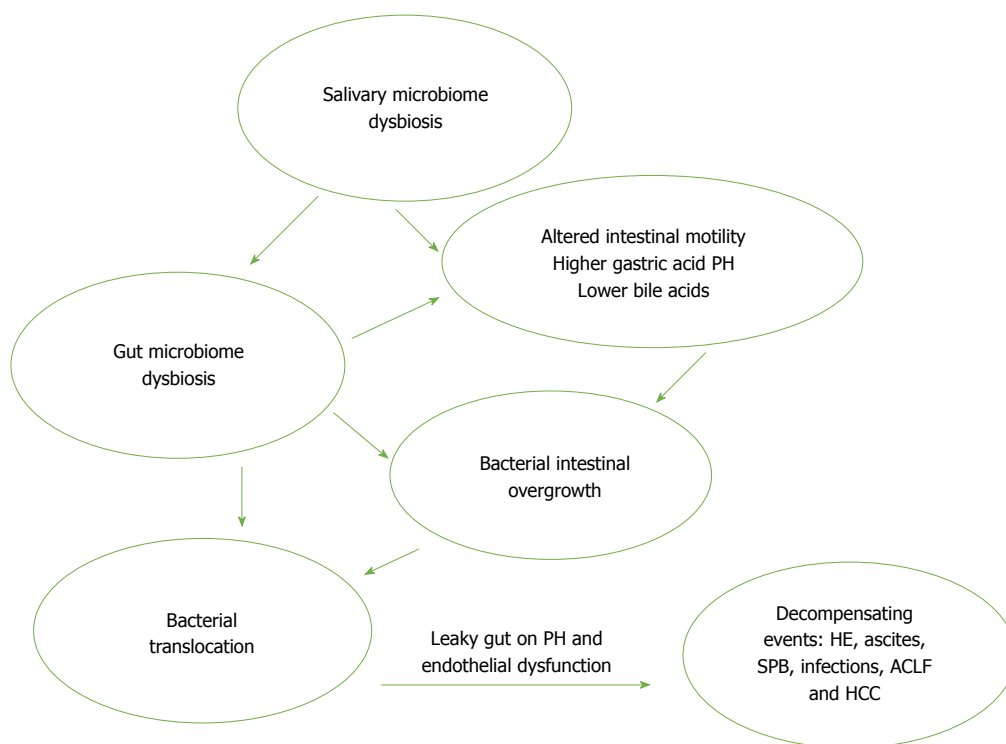
Portal hypertension, alterations in the intestinal microbiota, inflammation and oxidative stress can affect intestine barrier function, which becomes more permeable<sup>[24]</sup>. Eventually, pathologically increased BT from the gut to mesenteric lymph nodes arise in cirrhosis as an interplay of microbiome, deficiencies in secretory and mechanical intestinal barrier functions along with immune tolerant and deficient gut-associated lymphatic tissue. Small intestine has been suggested as the predominant site of BT in cirrhosis and SIBO has the greatest potential for promoting BT<sup>[25]</sup>.

More recent data raise implications on buccal origin of the gut microbiome supporting the emerging role of oral-liver-gut axis in decompensated cirrhosis<sup>[26]</sup>. Generally, oral dysbiosis has been correlated with local and distal infections, postulating that a baseline for the healthy core oral microbiota provides an opportunity to examine shifts during the onset and recurrence of disease<sup>[27]</sup>. Research findings imply a link between dental infections and accelerated progression of liver diseases trying to understand the clinical significance of oral-derived endotoxemia/bacteremia in the course of liver disease<sup>[28]</sup>.

A first study on omeprazole in compensated cirrhotics showed that gastric acid suppression allows intestinal overgrowth of bacteria normally present in the oral cavity and implicated a link between the gut microbiota changes and complications of cirrhosis<sup>[29]</sup>. Later, Bajaj *et al.*<sup>[14]</sup> found that dysbiosis, represented by reduction in autochthonous bacteria, is present in both saliva and stool in patients with cirrhosis. The major change of the gut microbiota was considered to stem from a massive invasion of the gut by oral bacterial species<sup>[13]</sup>. This link between the liver and the oral cavity could be *via* the gut through impaired intestinal permeability that in turn could allow direct translocation of bacteria and/or their products and inflammatory mediators from the oral cavity to the systemic circulation<sup>[26]</sup>. Patients with cirrhosis have salivary and enteric dysbiosis along with small bowel bacterial overgrowth, and translocation across the leaky gut. The latter is exacerbated by underlying portal hypertension and endothelial dysfunction and is associated with the development of decompensating complications<sup>[4]</sup> (Figure 1).

## **CLINICAL IMPACT OF THE ALTERED MICROBIOME**

Considering its key role in bacterial translocation, gut



**Figure 1 Pathophysiological mechanism showing the role of microbiome over the oral-gut-liver axis.** (Arrows imply the successive steps over the pathophysiology of complications.) PH: Portal hypertension; HE: Hepatic encephalopathy; SBP: Spontaneous bacterial peritonitis; ACLF: Acute-on-chronic liver failure; HCC: Hepatocellular carcinoma.

microbiome has been implicated in the pathogenesis of complications on the course of decompensated cirrhosis<sup>[21]</sup>. This culminates in systemic inflammation and endotoxemia, which induces innate immune dysfunction predisposing to infection, and development of acute conditions, such as hemorrhage, sepsis, and hepatic encephalopathy<sup>[4]</sup>.

### Hepatic encephalopathy

Dysbiosis, or altered microbiota represented by reduction in autochthonous bacteria, is present in both saliva and stool in patients with cirrhosis<sup>[14]</sup>. After HE development, there is significant change in microbial relative abundance<sup>[12]</sup>. Interestingly, two consecutive studies analyzed the correlation of certain bacterial families with cognition in cirrhotics. Stool microbiome analyses along with magnetic resonance imaging (MRI) brain assessment, revealed that specific bacterial taxa are associated with astrocytic changes and neuronal changes in humans with cirrhosis and HE in accordance with the clinically impaired cognition<sup>[30,31]</sup>. Indeed, patients with HE presented with altered flora (higher *Veillonellaceae*), poor cognition, endotoxemia, and inflammation (IL-6, TNF- $\alpha$ , IL-2, and IL-13) compared with cirrhotics without HE<sup>[30]</sup>. Healthy controls had a significantly higher proportion of autochthonous bacterial families than cirrhotics. Similarly cirrhotic patients with HE had a higher relative abundance of autochthonous families and a higher abundance pattern of *Staphylococcaceae*, *Enterococcaceae*, *Porphyromonadaceae* and *Lactobacillaceae* compared to

controls and cirrhotics without HE<sup>[31]</sup>.

Salivary and gut microbiome dysbiosis along with small bowel bacterial overgrowth and translocation of bacteria and their products across the leaky gut epithelial barrier underpin the endotoxemia and systemic inflammatory response that predispose to the manifestation of covert and overt HE<sup>[32]</sup>. Moreover, microbiome variations have associations with systemic inflammation and ammonia levels<sup>[31]</sup> and contribute to the development of HE by means of *ammoniogenesis* and generation of endotoxin-driven inflammatory response<sup>[18]</sup>. These microbial functions enriched in the microbiota in patients with cirrhosis supports the concept that the microbiome contributes to HE<sup>[33]</sup>. The enrichment of the modules for ammonia production gut bacteria might contribute to increased levels of ammonia in blood. Manganese-related transport system modules enriched in patients possibly contribute to the changes in concentrations of manganese, which accumulated within the basal ganglia in patients with end-stage liver disease and may have a role in hepatic encephalopathy. Modules for GABA biosynthesis enriched in patients are involved in the pathogenesis of hepatic encephalopathy too<sup>[13]</sup>.

### Ascites-infections-SBP-acute on chronic liver failure

One recently published study shed light in the role of microbiome in patients with ascites. Santiago *et al*<sup>[34]</sup>, found that specific serum microbiome is linked to the presence of ascites and proposed that these patients might have a greater deterioration of the intestinal barrier



integrity, also a higher degree of microbial translocation thus leading to a higher microbial diversity in serum.

In general, stool and saliva dysbiosis with reduction of autochthonous bacteria in patients with cirrhosis incites a systemic proinflammatory milieu due to changes in bacterial defenses<sup>[14]</sup>. Buccal proinflammatory environment in accordance with impaired local innate defenses of the oral cavity, represents a global mucosal-immune interface change in cirrhosis affecting the gut microbiota<sup>[4]</sup>. Moreover, pathologic bacterial translocation is associated with higher risk of developing infections; bacterial overgrowth, increased intestinal permeability, and integrity of immune surveillance mechanisms that allow bacteria (or parts of bacteria) to translocate to mesenteric lymph nodes and the systemic circulation, are important in driving SBP, in particular<sup>[18,21]</sup>.

Progressive severe changes in the gut microbiome present in cirrhotic patients on acute on chronic liver failure<sup>[12,35]</sup>. Changes in salivary and stool microbiota have been independently associated with the prediction of hospitalizations in cirrhotic patients<sup>[14,36]</sup>. Besides, the great interest regarding microbiota has been shifting from pathogenesis toward the prediction of clinically relevant outcomes in cirrhosis<sup>[5]</sup>.

### HCC

In 2016, Lu *et al.*<sup>[17]</sup> identified oral microbiota dysbiosis in cirrhotic patients with liver carcinoma recognizing specific discriminatory bacteria that could provide novel and non-invasive diagnostic biomarkers of the presence of liver carcinoma. The suggested pathogenic pathway introduced the role of endotoxemia produced by gut microbiota; associated with oncogenic pathways when increased promotes the development of hepatocarcinogenesis<sup>[37]</sup>. Experimental animal models support this promoting effect of the gut microbiota-driven inflammation in hepatocarcinogenesis<sup>[38]</sup>, though data on human are scarce; Zhang *et al.*<sup>[39]</sup> demonstrated that the induction of dysbiosis, with increased growth rate of *E. coli* and *Atopobium* cluster and significantly decreased percentages of benign bacteria (*Lactobacillus* group, *Bifidobacterium* group, and *Enterococcus* group), is sufficient to promote hepatocarcinogenesis by enhanced portal LPS levels. So, there is profound impact of intestinal microbiota and gut homeostasis on HCC development<sup>[40]</sup> (Table 1).

## THERAPEUTIC ASPECT OF MICROBIOME

Overall, the contribution of the microbiota to pathogenesis becomes more pronounced with progressive disease and therefore remains an important therapeutic target in the management of cirrhosis<sup>[18]</sup>. The mutual interdependence between the pathogenesis of the cirrhotic process, intestinal bacterial translocation and portal pressure makes the gut–liver axis an attractive target for specific therapeutic interventions<sup>[19]</sup>. The gut microbiome can be modulated in different ways, using

prebiotics, probiotics, synbiotics, antibiotics, and even fecal microbiota transplantation<sup>[41]</sup>.

Lactulose is probably the best-studied prebiotic in liver disease and is commonly used for the treatment of HE<sup>[41]</sup>. It acts by acidifying and modifying the colonic flora. This could lead to a displacement of urease-producing bacteria with non-urease-producing *Lactobacillus*, and, therefore, to a reduction in the formation of potentially toxic short-chain fatty acids<sup>[19]</sup>. Probiotics are living microorganisms that confer a health benefit on their host through antimicrobial effects, enhancement of mucosal barrier integrity, and immunomodulation<sup>[41]</sup>. Probiotics and synbiotics (a combination of probiotics and prebiotics in a form of synergism) have been used broadly in trials addressing HE, showing improvements in endotoxemia, endothelial dysfunction, and dysbiosis, along with modifications on bile acid pool composition; though larger clinical trials with clinically significant outcomes are needed<sup>[19]</sup>.

The traditional and most logical first approach to diminish translocation of microbial components and products is to reduce the enteric burden of the bacteria that contribute the most to this, with antibiotics<sup>[20]</sup>. Rifaximin, a minimally-absorbed oral antimicrobial agent, has been intensively studied on advanced liver cirrhosis. It is supported that rifaximin diminishes the risk of HE recurrence and HE-related hospitalizations but also improves endotoxemia, systemic hemodynamics and renal function<sup>[23]</sup>. Finally, new perspectives came from fecal microbiota transplant, which seems to influence the microbiota through limiting the colonization of pathogens and affecting microbial metabolic function<sup>[41]</sup>. In a latest mouse study the gut microbiota was reprogrammed by transplanting bacteria with minimal urease gene content, thus reduction in fecal urease activity. This led to reduced fecal ammonia levels, and neurobehavioral deficits and decreased the morbidity and mortality associated with liver damage<sup>[42]</sup>.

## CONCLUSION

Microbiome has been rather implicated in the pathogenesis of various clinical conditions ranging from chronic liver diseases to decompensated complications<sup>[5,43-45]</sup>. Several studies presented different aspects of the altered microbiome seen in patients with cirrhosis. There is no consensus among the researchers. Specifically, microbiome dysbiosis has been introduced either as a reduced ratio of autochthonous to non-autochthonous taxa (CDR) or as inversion of the *Firmicutes/Bacteroidetes* ratio<sup>[12,14,16]</sup>. Whatever the expression, salivary and stool dysbiosis has been described as an interplay in the development of cirrhosis-related complications. Besides, modulation of the microbiome with the existing therapeutic strategies remains the cornerstone of the management of cirrhosis. Thus, estimation of microbiome in patients with cirrhosis seems to facilitate new prognostic and therapeutic strategies.

**Table 1** Published studies regarding microbiome over cirrhotic patients

Study	Analysis	Conclusion
Chen <i>et al</i> <sup>[10]</sup> , 2011	36 patients with liver cirrhosis and 24 healthy controls; analysis of fecal microbial community	Fecal microbial communities are distinct in patients with cirrhosis compared with healthy individuals. The prevalence of potentially pathogenic bacteria, such as <i>Enterobacteriaceae</i> and <i>Streptococcaceae</i> , along with the reduction of beneficial populations such as <i>Lachnospiraceae</i> in patients with cirrhosis may affect prognosis
Bajaj <i>et al</i> <sup>[11]</sup> , 2012	60 patients with cirrhosis (24 patients without HE/36 with HE) and 17 age-matched healthy controls; stool and colonic mucosal microbiome analysis, linkage of them with changes in peripheral inflammation and cognition	There was higher abundance of autochthonous genera and a lower abundance of potentially pathogenic ones in controls compared with cirrhotic patients' mucosa. Significant change was recorded in the microbiome of the mucosa compared with stool. In general HE patients had less "healthy" microbiome
Bajaj <i>et al</i> <sup>[30]</sup> , 2012	25 patients (17 HE and 8 without HE) and 10 controls; fecal microbiota analysis	Cirrhosis, especially when complicated with HE, is associated with significant alterations in the stool microbiome compared with healthy individuals. Specific bacterial families ( <i>Alcaligenaceae</i> , <i>Porphyromonadaceae</i> , <i>Enterobacteriaceae</i> ) are strongly associated with cognition and inflammation in HE.
Bajaj <i>et al</i> <sup>[29]</sup> , 2014	15 patients with compensated cirrhosis and 15 age-matched healthy controls; stool microbiota profiling before (pre) and after PPI	Significant microbiota change was seen in both controls and cirrhotics after omeprazole. Omeprazole is associated with a microbiota shift and functional change in the distal gut in patients with compensated cirrhosis that could set the stage for bacterial overgrowth
Bajaj <i>et al</i> <sup>[12]</sup> , 2014	219 cirrhotics (121 compensated outpatients, 54 decompensated outpatients, 44 inpatients) and 25 age-matched controls; stool analysis and introduction of the cirrhosis dysbiosis ratio (CDR)	Relative stability of the microbiota and CDR over time within cirrhotics whose disease remained unchanged. Microbiota changed when the underlying disease worsened in HE and infections reflected by CDR reduction. Associations of increased dysbiosis, with lower CDR and higher gram-negative taxa relative abundance. CDR for controls was significantly higher compared to all cirrhotic patients
Kakiyama <i>et al</i> <sup>[45]</sup> , 2014	19 healthy, 6 drinkers without liver disease, and 78 cirrhotic (compensated and decompensated) patients; fecal and serum bile acids (BA), serum endotoxin, and stool microbiota analysis	Bile acids affect the composition of the intestinal microbiota Higher total BA pool in alcoholic cirrhotics could lead to a higher substrate for microbiota.
Qin <i>et al</i> <sup>[13]</sup> , 2014	98 cirrhotic patients and 83 healthy controls; gene catalogue of gut microbes analysis	Inflammation and gut barrier injury in alcoholic liver disease Patients with liver cirrhosis have a less "healthy" gut microbiome, enriched with <i>Veillonella</i> , <i>Streptococcus</i> , <i>Clostridium</i> . Healthy individuals' microbiome was enriched with autochthonous species ( <i>Lachnospiraceae</i> and <i>Ruminococcaceae</i> ). Proof that the major change of the gut microbiota in patients with liver cirrhosis, is mainly because of a massive invasion of the gut by oral bacterial species
Bajaj <i>et al</i> <sup>[14]</sup> , 2015	102 patients with cirrhosis (with/without HE) and 32 age-matched healthy controls; stool and saliva microbiome analysis along with evaluation of systemic and salivary inflammatory response	Dysbiosis, represented by reduction in autochthonous bacteria ( <i>Lachnospiraceae</i> , <i>Ruminococcaceae</i> , and <i>Clostridiales</i> XIV), is present in both saliva and stool in patients with cirrhosis, compared to controls. Stool cirrhosis dysbiosis ratio ( <i>Lachnospiraceae</i> + <i>Ruminococcaceae</i> + <i>Clostridiales Incertae Sedis</i> XIV + <i>Veillonellaceae</i> / <i>Enterobacteriaceae</i> + <i>Bacteroidaceae</i> ) was significantly lower in patients with cirrhosis. Salivary microbiota dysbiosis ratio ( <i>Lachnospiraceae</i> + <i>Ruminococcaceae</i> + <i>Clostridiales Incertae Sedis</i> XIV/ <i>Streptococcaceae</i> ), was lower in patients with cirrhosis, compared to controls
Bajaj <i>et al</i> <sup>[36]</sup> , 2015	278 cirrhotics (39% with HE, 31% with DM); stool microbial analysis and 72 underwent mucosal analyses	Cirrhotic subjects who required non-elective 90 d hospitalization had a different microbial profile DM in the presence of cirrhosis alters the mucosal and stool microbiota compared to cirrhotics without DM, it does not add to the 90 d hospitalization risk
Chen <i>et al</i> <sup>[35]</sup> , 2015	79 ACLF patients and 50 controls; fecal microbiota analysis	ACLF patients had lower abundance of <i>Bacteroidaceae</i> , <i>Ruminococcaceae</i> , and <i>Lachnospiraceae</i> , but higher abundance of <i>Pasteurellaceae</i> , <i>Streptococcaceae</i> , and <i>Enterococcaceae</i> . Abundance of <i>Lachnospiraceae</i> was decreased in ACLF patients with HE. Gut dysbiosis in ACLF has predictive value for mortality and could represent diagnostic biomarker
Ling <i>et al</i> <sup>[16]</sup> , 2015	10 CHB patients, 10 patients with HBV-associated compensated liver cirrhosis (LC), and 10 healthy controls (HC)	Differences in the compositions of the oral microbiota revealed the dysbiosis involved in the development of HBV-CLD
Lu <i>et al</i> <sup>[17]</sup> , 2016	35 early liver carcinoma (LC) patients with cirrhosis and 25 matched healthy subjects; study of microbiome of the tongue coat	Certain key bacterial species may characterize LCT microbiota; <i>Oribacterium</i> and <i>Fusobacterium</i> could distinguish LC patients from healthy subjects. Microbiota dysbiosis of tongue coat in LC patients, may provide novel and non-invasive potential diagnostic biomarker of LC.

Ahluwalia <i>et al</i> <sup>[31]</sup> , 2016	40 healthy controls and 147 cirrhotics (85 cirrhotic patients had HE); stool samples and brain MRI assessment	Effort to understand the role of impaired gut-liver-brain axis in cirrhosis.  Gut microbial changes are linked with systemic inflammation, ammonia and ultimately with neuronal and astrocytic dysfunction in cirrhotic patients, especially those with HE
Chen <i>et al</i> <sup>[15]</sup> , 2016	30 cirrhotic patients and 28 healthy subjects; study of the duodenal microbiome	Duodenal mucosa microbiota in cirrhotic patients is dramatically different from healthy controls.  The duodenum dysbiosis might be related to alterations of oral microbiota and changes in duodenal micro-environment. Possible associations between small intestinal microbiota of oral origins and hepatic encephalopathy.
Santiago <i>et al</i> <sup>[34]</sup> , 2016	27 patients (13 with ascites and 14 without ascites), 17 healthy controls; stool ( <i>n</i> = 17) and serum ( <i>n</i> = 7) microbiome analysis	Patients with ascites have a greater deterioration of the intestinal barrier integrity, also a higher degree of microbial translocation than those without ascites, thus leading to a higher microbial diversity and higher concentration of lipopolysaccharide binding protein (LBP) in serum  Specific serum microbiome is linked to the presence of ascites Alteration of the serum and fecal microbiome composition be considered indicators of cirrhosis progression

HE: Hepatic encephalopathy; PPI: Proton-pump inhibitor; CDR: Cirrhosis dysbiosis ratio; ACLF: Acute-on-chronic liver failure; HBV: Hepatitis B virus; CLD: Chronic liver disease; DM: Diabetes mellitus.

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