



# Narrative review of gut microbiota and liver diseases: facts and fictions

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**Background and Objective:** The close relationship of the liver to gut bacteria is widely recognized, studied, and constantly evolving. Evidence has shown that the alteration of the microbiome causes bacterial translocation, alteration of the composition of bile acids and increased intestinal permeability, generating the activation of several inflammatory pathways within the liver. This chronic inflammation associated with intestinal dysbiosis is believed to play a crucial role in the progression of chronic liver disease (CLD) (cirrhosis, hepatic steatosis, autoimmune diseases such as primary biliary cirrhosis, sclerosing cholangitis) and their complications (hepatic encephalopathy, hepatocarcinoma). In this review, we aim to describe the current facts of the composition of the microbiota and its effect on the development and progression of CLD, we also present the relationship of the microbiota with other pathologies (such as cardiovascular, endocrinological).

**Methods:** A literature search was conducted in PubMed/Medline, and Google Scholar (prior to October 31, 2021) to retrieve relevant articles of this topic. Only English and Spanish language articles and published after 1995 were considered. We performed a bibliographic review of the current knowledge on this topic to try to explain this association in more depth.

**Key Content and Findings:** The main facts found with strong evidence were that the colonization by the microbiota begins from birth, environmental factors are the most important for the differentiation of the microbiota, which explains the variability between individuals. Microbiota has metabolic, inflammatory and endocrinological function, and plays an important role in the pathogenesis of CLD development and progression. Hence, there still strong controversy whether dysbiosis is the etiological factor or is only a cofactor, and whether or not other microbiome component play a role in these diseases.

**Conclusions:** Current data on the role of the gut microbiota in CLD is constantly evolving and despite scientific evidence, it is not fully understood. More research is needed to better understand this association and its alterations in the microbiota and its effect on the various systems of the human body.

**Keywords:** Chronic liver disease (CLD); metabolic associated fatty liver disease (MAFLD); gut microbiota; bile acids; dysbiosis

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## Introduction

The gastrointestinal tract is colonized by a wide range of commensal microorganisms, approximately 100 billion (1) that play an important role in maintaining health. This intestinal microbiota represents 10 times more than the total number of cells in the human body. It is made up of bacteria, viruses and fungi, which are divided into 6 groups: Gram negative Bacteroidetes, Proteobacteria, Gram positive Firmicutes and Acinetobacteria, Fusobacteria and Verrucomicrobia (2). For all the genetic material of the microbiota, it has been called the second genome contained in the human body (1). The intestinal microbiota plays a key role in maintaining health condition and drives diverse immune, nutritional and metabolic functions within the host. Its composition and diversity vary according to different factors such as the form of birth (caesarean section or vaginal route), maternal microbiota, infant diet (breast milk or formula), geographic location, age, gender (3), diet in adulthood (meat-based or vegetarian/vegan), in addition to the use of antibiotics (2). The close relationship between the gut microbiota and the liver, formerly known as gut-liver axis, is widely studied, accepted but not fully understood (4). The alteration of the gut-liver axis due to intestinal dysbiosis, intestinal delayed transit, bacterial overgrowth of the small intestine (5) and increased intestinal permeability seen in chronic liver disease (CLD) provoke a chronic systemic inflammatory state, which drives the progression of CLDs (6). As shown in *Table 1* (7-9).

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dmr.amegroups.com/article/view/10.21037/dmr-21-85/rc>).

## Methods

A comprehensive research of Medline In-Process and other Non-Indexed Citations was conducted, using MEDLINE by the US National Library of Medicine National Institutes of Health and Google Scholar (prior to October 31, 2021) to retrieve relevant articles. Literature search was made using medical subject headings (MeSH) and text words related to microbiota and chronic liver disease. Controlled terms were used to search for studies (Chronic Liver disease [ALL] AND Microbiota), (Microbiota [ALL] AND bile acids), (microbiota [ALL] AND intestinal barrier), (Microbiota [ALL] AND metabolic disturbance), (Microbiota [ALL] AND systemic inflammation), (microbiota [ALL] autoimmune hepatitis, primary biliary

cirrhosis, primary sclerosing cholangitis), (microbiota [ALL] AND hepatic encephalopathy), (microbiota [ALL] AND Non-Alcoholic Fatty Liver Disease AND Alcoholic Liver Disease), (Microbiota [ALL] AND Hepatocellular carcinoma), (Microbiota [ALL] AND Acute-on-Chronic liver failure). Additional studies were located by manual search using references from retrieved articles. Research strategies were shown in *Table 2*.

## Intestinal mucosal immune barrier: first line of defense

The intestinal mucosa is constantly changing, with exchange of nutrients, ions, and fluids through the epithelium, but it is also in contact with many potentially pathogenic antigens and microorganisms. Its architecture is so elaborate that it has a contact surface of approximately 300–400 m<sup>2</sup>. It is colonized by bacteria in a range of 1×10<sup>4</sup> cells in the small bowel to 1×10<sup>14</sup> in the colon (10). The intestinal immune system is made up of 3 different structures: Peyer's patches, lamina propria, and the epithelium (mucosa-associated lymphoid tissue, MALT) (11). The mucosal layer produces glycoprotein, the main source of nutrition for some bacterial species, it also represents the main source of immunoglobulin A (IgA) and antimicrobial peptides, this helps to preserve intestinal integrity that protects against bacterial translocation. Another important anatomical component of the intestinal barrier is the tight junction (TJ) proteins that holds epithelial cells together while preserving the integrity of the intestinal barrier; when these proteins are under-expressed, an increase in the passage of lipopolysaccharide (LPS) and bacterial products from the bowel to the portal vein is observed (12). The second line of defense is the immune cells present in the intestinal barrier, composed mainly of lymphocytes, natural killer T cells, mononuclear phagocytes and dendritic cells. The presence of these immune cells is important to preserve intestinal homeostasis, avoiding an increase in intestinal permeability and the activation of inflammatory pathways (13) (*Figure 1*).

## Anatomic barriers of the mucosa

The anatomic barriers of the mucosa are composed by:

- (I) *Extracellular components*: most of the mucosal surface is hydrated by a gel layer formed by mucin, which is secreted by specialized epithelial cells such as gastric and intestinal foveolar mucous cells and goblet cells. This creates a barrier that prevents most

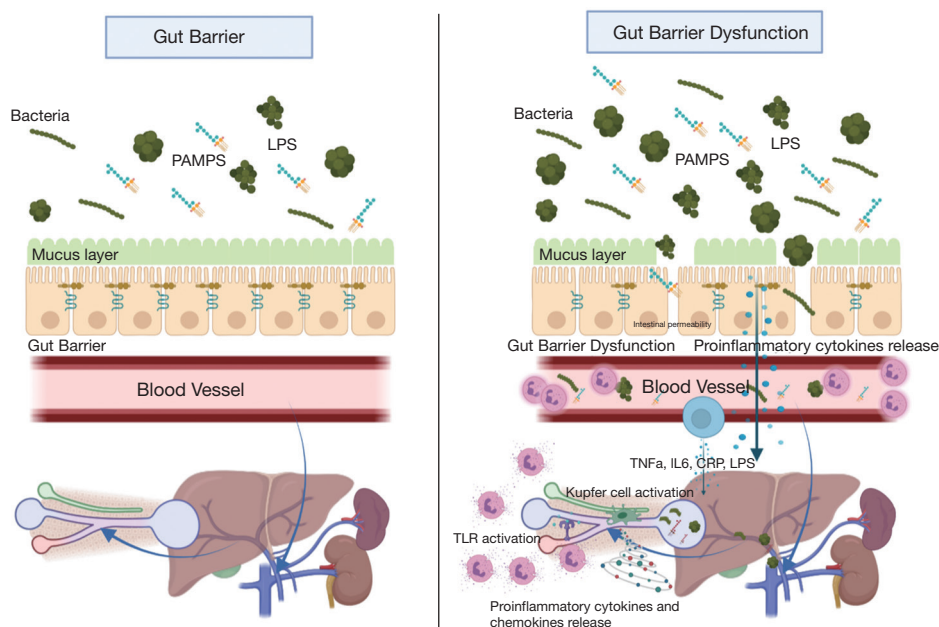
**Table 1** Characterization of the intestinal microbiota in different clinical conditions (7-9)

Clinical condition	Phylum	Species
Normal	Firmicutes, Bacteroidetes, Verrucombia Actinobacteria, Fusobacteria, Proteobacteria	Lactobacillus, Clostridium, Enterococcus, Ruminococcus, Bacteroides, Prevotella
Obesity	Firmicutes (↑), Mitsukella (↑), Bacteroidetes (↓), Bifidobacterium (↓), Odoribacter (↓), Phascolartobacterium (↓), Oscillospira (↓)	<i>Akkermansia muciniphila</i> (↓), Tuminococcaceae, Rikenellaceae, Mollicutes (↑), Alistipes (↑), Bilophila (↑), Roseburia, <i>Eubacterium rectale</i> (↓), <i>Rominococcus bromii</i> (↓)
Diabetes	T2DM: Firmicutes (↑), Lactobacillus (↓) Bacteroidetes (↓)	T2DM: Roseburia (↓), <i>Faecalibacterium prausnitzii</i> (↓), <i>E. coli</i> (↑), Ruminococcus (↓), <i>Akkermansia muciniphila</i> (↓), Clostridium (↓)
	T1DM: Parabacteroides	T1DM: Parabacteroides (↓), <i>Akkermansia muciniphila</i> (↓), <i>E. coli</i> (↑)
MAFLD	Acidaminococcus (↑), Akkermansia (↑), Allisonella (↑), Anaerococcus (↑), Bradyrhizobium (↑), Dorea (↑), Escherichia (↑), Parabacteroides (↑), Robinsonella (↑), Alistipes (↓) Anaerosporobacter (↓), Coprobacter (↓), Moryella (↓), Subdoligranulum (↓)	Veillonella (↑), <i>E. lenta</i> (↑), <i>C. clostridioforme</i> (↑), <i>C. ramosum</i> (↑), <i>Lachnospiraceae bacterium</i> (↑), <i>Barnesiella intestinhominis</i> (↑), <i>Faecalibacterium prausnitzii</i> (↓), <i>E. rectale</i> (↓), <i>C. coccooides</i> (↓)
Cancer	Firmicutes (↓), Proteobacteria	<i>Bilophila wadsworthia</i> , <i>Fusobacterium nucleatum</i> (↑)

MAFLD, metabolic associated fatty liver disease.

**Table 2** The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	From October 1 <sup>st</sup> to 31 <sup>st</sup> 2021
Databases and other sources searched	Pubmed/Medline, Google Scholar and Cochrane
Search terms used (including MeSH and free text search terms and filters)	Controlled terms were used to search for studies (Chronic Liver disease [ALL] AND Microbiota), (Microbiota [ALL] AND bile acids), (microbiota [ALL] AND intestinal barrier), (Microbiota [ALL] AND metabolic disturbance), (Microbiota [ALL] AND systemic inflammation), (microbiota [ALL] autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis), (microbiota [ALL] AND hepatic encephalopathy), (microbiota [ALL] AND Non-Alcoholic Fatty Liver Disease AND Alcoholic Liver Disease), (Microbiota [ALL] AND Hepatocellular carcinoma), (Microbiota [ALL] AND Acute-on-Chronic liver failure). Additional studies were located by manual search using references from retrieved articles
Timeframe	1995–2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Research studies, randomized or non randomized trials and reviews/meta-analysis. We excluded studies that were not in English or Spanish Language, or that were published before 1995. We excluded citations that were not completely related to the topic or that did not have an abstract available or that we do not have access to the full text. A total of 200 articles were obtained. We decided to include 80 articles that fulfilled the inclusion criteria
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The research was performed by the main author, the selection was confirmed by all the authors of the manuscript
Any additional considerations, if applicable	None



**Figure 1** Relationship between the microbiota and the intestinal barrier (10-20). **Gut Barrier:** Under normal conditions, the microbiota is in close contact with the intestinal epithelium, bacterial translocation is diminished by the mucus layer and cell junctions. **Dysfunction of the intestinal barrier:** Many factors intervene in the dysfunction of the intestinal barrier, such as dysbiosis, being one of the main ones, this causes there to be contact between the microbiota and its waste products such as toxins and lipopolysaccharides. When there is an anatomical alteration, the permeability increases, allowing these products to pass into the bloodstream, where they provoke an immune response mediated mainly by T lymphocytes, systemically releasing pro-inflammatory cytokines such as tumor necrosis factor alpha, IL 6, lipopolysaccharides and protein. C-reactive, through the blood flow reaches the liver where it has been shown that they interfere with the progression of different liver entities such as cirrhosis, hepatic steatosis, MAFLD, ALD). This can affect other organs. TNF, tissue necrosis factor; IL 6, interleukin 6; CRP, C-reactive protein; ALD, alcoholic liver disease; MAFLD, metabolic associated fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; LPS, lipopolysaccharide.

bacteria from coming into direct contact (14). The importance of this is shown in pathologies such as cystic fibrosis, in which the hyperviscous production of mucus contributes to infectious pulmonary, pancreatic and intestinal pathologies (15).

- (II) *Cellular components:* made up of specialized epithelial cells, which are interconnected by junctions and are covered by mucus and bactericidal peptides. This allows a small number of bacteria to penetrate the intestinal epithelium; however, there are many physical and pharmacological agents that can harm it (16). The microbiota and the intestinal mucosa are in constant interaction to maintain homeostasis. When the balance is broken, it predisposes to different diseases (11).

### Interplay between the gut microbiome and the liver

The relationship between the microbiota and the progression of CLD is continuously investigated, constantly evolving and not completely understood, extensive scientific evidence is still missing to fully understand the importance of the microbiota and liver disease. Current data have shown that patients with liver cirrhosis have increased bacteremia and increased levels of lipopolysaccharides, as well as increased intestinal permeability (6). Primary human bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized in the liver, secreted into the intestine, and undergo bacterial biotransformation to generate secondary bile acids, lithocholic acid (LCA) and deoxycholic acid (DCA) by the

bile salt hydrolase (BSH) (17). The circulation of secondary bile acids from the intestine to the liver activates the farnesoid X receptor (FXR) that suppresses the production of bile acid. Intestinal FXR seems to modulate gut microbiota by inducing Acetatifactor (Clostridium cluster XIV family) and Bacteroides to convert primary bile acids into secondary bile acids that activate takeda G coupled receptor 5 (TGR5) which in turn stimulates the secretion of glucagon like peptide 1 (GLP1) improving hepatic metabolism and insulin sensitivity (18,19). The primary classes of such receptors include the Toll-like (TLR) and NOD-like (NLR) receptors that recognize a variety of bacterial products, including LPS, flagellin, peptidoglycan, and bacterial DNA. The main consequence of TLR/NLR detecting its cognate agonists is to widely induce host-defense gene expression that can protect against numerous microbes. Numerous studies indicate that, like most macrophages populations, Kupffer cells respond to very low concentration of LPS by activating NF- $\kappa$ B and producing pro-inflammatory cytokines, suggesting that these cells would respond at physiologically relevant levels of microbial products that reach the liver (20).

### New insights on gut microbiota in liver disease

The liver has a double blood supply, almost 70% of its blood comes from the intestines through the portal circulation and the rest through the hepatic artery. Although the intestinal mucosa acts as an effective barrier against the translocation of microbes and microbial products from the gut to the circulation, small amounts of these enter the portal venous blood. The liver, strategically located between highly contaminated bowel and sterile systemic circulation, functions as a filter. The proposed mechanisms of gut–liver interaction in these diseases include alterations in composition of the gut microbiota, bacterial overgrowth of the small intestine, increased permeability of the small bowel and alterations in mucosal and systemic immunity. With the development of better technology, such as genetic sequencing analysis, it is possible to classify bacteria based on DNA sequence. It has been recognized that short-chain fatty acids such as butyric acid, acetic (microbiota fermentation) can decrease the T-cell-mediated immune response through an epigenetic mechanism (17,21). Probiotics have also been used in murine hepatocellular carcinoma (HCC) models to oppose dysbiosis and have shown a reduction in HCC development (17).

Although research has traditionally focused on the

bacterial component of the gut microbiota, research of enteric fungal and viral species has increased due to advances in sequencing and analysis technologies (21,22).

### Microbiota and metabolic disturbance

Dysbiosis has been associated with important metabolic consequences, such as increased expression of genes that encode enzymes related to carbohydrate metabolism, closely related to the development of metabolic associated fatty liver disease (MAFLD) (23).

### Diabetes mellitus type 2

Alterations in glucose metabolism (glucose intolerance and type 2 diabetes mellitus) represent pathologies with a high prevalence; in 2012 it was estimated that approximately 9.3% (29.1 million people) in the United States have type 2 diabetes mellitus. The role of dysbiosis in the intestinal microbiota has recently been investigated, which could play an important role in pathogenesis. Different observational studies have described differences between the microbiota of people with type 2 diabetes mellitus versus healthy people (24). Opportunistic pathogens are frequently described in T2DM microbiota communities, including the species *Clostridium ramosum*, *hathewayi* and *symbiosum*, *Bacteroides caccae*, *Eggertbella lenta* and Butyrate-producing microbes are particularly depleted specifically in the Clostridiales order, including the genera Ruminococcus and Subdoligranulum, and the species *Eubacterium rectale*, *Faecali prausnitzii*, *Roseburia intestinalis* and *Roseburia inulinivorans*, pre-diabetic patients also demonstrate similar findings in their microbiota communities, including a decrease in microbial diversity; depletion in the numbers of the genera Akkermansia and Clostridium; and increase in Ruminococcus and Streptococcus (25).

There are different mechanisms that have been proposed through which the microbiota alters glucose metabolism:

- (I) *Production of metabolites*: short chain fatty acids (SCFAs; butyrate mainly produced mainly by Firmicutes and acetate produced by Bacteroidetes) are the main products resulting from anaerobic fermentation of dietary fiber and have a direct impact on the hepatic metabolism of glucose, decreasing glycolysis and gluconeogenesis, increasing glycogen synthesis.
- (II) *Stimulation of the GPR41 receptor* by butyrate and propionate can induce intestinal gluconeogenesis,



promoting the secretion of the incretin GLP-1 (25). Better HbA1c control (<7%) has been described in patients who receive fiber in the diet compared to the control group, as well as the consumption of a Mediterranean diet that improves glucose sensitivity in patients with high cardiovascular risk. This is due to the production of large amounts of succinate by bacterial fermentation of dietary fiber which improves glycemic control through the activation of intestinal gluconeogenesis (26,27).

### Type 1 diabetes mellitus

It is an autoimmune disease in which pancreatic destruction of B cells causes insulin deficiency resulting in hyperglycemia and risk of ketoacidosis. The presence of 5 bacterial genera has been identified with the development of type 1 diabetes mellitus, mainly Parabacteroides. A decrease in the production pathways of short-chain fatty acids such as butyrate has been documented in patients who develop antibodies against pancreatic islets (28,29).

### Microbiota and cardiovascular risk

Many researchers have reported the association between cardiovascular risk and the microbiota. Bacterial DNA has been detected in atherosclerotic plaques. Elevated levels of lipopolysaccharides produced by the bacterial wall of the microbiota have been linked to modulation of inflammation, immunity and vascular function. Patients with decompensated heart failure have higher blood endotoxin levels compared to stable patients (30,31). The strongest evidence for the relationship between the microbiota and cardiovascular risk is related to the microbial metabolism of dietary factors such as carnitine and choline. These metabolites are potentially the cause of atherosclerosis. Trimethylamine is produced by the microbiota from nutrients containing L-carnitine, which promotes the formation of foam cells and atheroma plaques in animal models (32). Many microorganisms such as *Chlamydomphila pneumoniae*, *Porphyromonas gingivalis*, *Helicobacter pylori*, Influenza A virus, Hepatitis C virus, cytomegalovirus, and human immunodeficiency virus have been associated with an increased risk of cardiovascular disease. Infections contribute to atherosclerosis through two predominant mechanisms: direct infection of the blood vessel wall (making it prone to plaque formation), or indirectly with an infection at a distant site by promoting proinflammatory mediators of a systemic immune response that predispose to

plaque growth (33).

### Microbiota and systemic inflammation

The microbiota has a variety of functions that play a role in its ability to grow and colonize. Related mechanisms have been proposed between the microbiota and inflammatory markers, among them:

- (I) Lipopolysaccharides, also known as endotoxins, are found as a component of the cell wall of Gram-negative bacteria. Its increased values have been reported in obesity, metabolic disorders, tissue inflammation and pancreatic dysfunction (34). Under normal conditions, the intestinal barrier can minimize the translocation of LPS from the intestinal lumen to the circulation. Due to the dysfunction of the intestinal barrier by diet, the microbiota allows the movement of LPS producing a systemic immune response mediated by Toll receptors (TLR 4) (35).
- (II) SCFAs. Bacteria can metabolize complex carbohydrates to SCFAs (30,31), SCFAs play an important role in reducing the activation of the inflammatory cascade. Among them, butyrate is an anti-inflammatory metabolite, which reduces the risk of developing insulin resistance, it also reduces the translocation of LPS. *Faecalibacterium prausnitzii* was identified as a butyrate-producing bacterium, a significant decrease of this microorganism has been documented in obese individuals (34).
- (III) C-reactive protein (CRP). It is an acute phase reactant, associated with cardiovascular disease, obesity and type 2 diabetes. The genus *Phascolarctobacterium* has been associated with low levels of CRP, this relationship may explain why the decline of the genus has been associated with inflammation of the colon. *Phascolarctobacterium* are producers of propionate, a short-chain fatty acid that inhibits the inflammatory response. *Faecalibacterium* levels are inversely correlated with CRP levels (34).

### Effect of microbiota in CLD progression and complications

#### Alcoholic liver disease (ALD)

Alcohol-related CLDs are responsible for 0.9% of all deaths and 47.9% of all deaths attributable to cirrhosis. Chronic alcohol intake allows intestinal bacteria overgrowth and

dysbiosis in humans and animals. In humans, it is defined as the growth of at least  $1 \times 10^5$  in a bean aspirate culture. Chronic alcohol consumption decreases intestinal levels of antimicrobial-regenerating islet-derived (REG)-3 lectins. Specific intestinal deficiency in Reg3b or Reg3g increases the number of intestinal bacteria and their translocation to mesenteric lymph nodes and the liver causing the development and progression of ethanol-induced steatohepatitis. In contrast, Reg3g overexpression in the intestinal epithelium protects animals from ethanol-induced liver injury (36). Patients with ALD have dysbiosis, represented by a reduction of the mean abundances of Bacteroidetes and an increase in Proteobacteria. Patients with alcohol-related liver cirrhosis have been documented to have a reduction in species as *Lachnospiraceae*, *Lactobacillus* spp, *Bifidobacterium* spp, *Ruminococcaceae*, Clostridiales XIV, and an increase in Enterobacteriaceae, including the predominant genus *Escherichia coli*, Bacteroidaceae (37). Gut bacteria have also been reported to differ between stages of ALD and are associated with its progression. *Streptococcus* have been associated with the severity and progression of ALD (38). Bacteria of the *Lactobacillus* and *Veillonella* genera have also been reported to increase in patients with alcoholic hepatitis (AH), mainly in severe cases; on the other hand, bacteria as *Eubacterium*, *Oscillibacter*, *Prevotella*, *Prevotellaceae* and Clostridiales are reduced in patients with severe AH (39).

### MAFLD

It is considered one of the main causes of CLD in the general population. It is a disease with a wide clinical spectrum that ranges from steatohepatitis, fibrosis, cirrhosis and/or HCC. The most serious form is steatohepatitis and it can progress to cirrhosis in 20% of patients (40). The profile of microorganisms present in fatty liver disease is frequently associated with obesity and excess abdominal adiposity, there is a decrease in diversity compared to healthy people (41). An increase in the radius of Firmicutes/Bacteroidetes is reported, with an increase in Bacteroidetes and a decrease in Firmicutes. Numerous pathophysiological mechanisms have attempted to explain the relationship between the microbiota and liver-systemic inflammation. The importance of increase in intestinal permeability has been described, causing with the continuous passage of LPS and pathogen associated molecular patterns (PAMPS) through the portal vein causing endotoxemia and immune dysregulation, together with the bacterial overgrowth

(SIBO) that occurs (42). All of the aforementioned causes the activation of inflammatory pathways with the activation of Toll-like receptors and the secretion of cytokines, interleukin 8 (IL8), IL6 and  $TNF\alpha$ , enhancing liver inflammation (steatohepatitis), fibrosis and systemic inflammation (43) (Figure 2).

Endogenous ethanol (EnEth) producing bacteria have been shown to play a role in the onset and exacerbation of various stages of MAFLD (8). EnEth production is increased, and the prevalence of intestinal permeability and bacterial translocation is higher, the *Klebsiella pneumoniae* strain (W14) with high alcohol production (HiAlc) was isolated from the feces of a patient with severe non-alcoholic steatohepatitis. W14 was considered the potential culprit for MAFLD, which leads to hepatic steatosis and mitochondrial dysfunction (44). Studies have shown that Enterobacteriaceae, Proteobacteria, and *Escherichia* were the only phylum, family, and genus types exhibiting significant differences in obese subjects with or without steatohepatitis, and steatohepatitis microbiomes exhibited a lower percentage of Bacteroidetes (36). Interestingly, MAFLD patients have increased concentrations of *Bacteroides* and *Ruminococcus* and a reduction of *Prevotella* mainly in advanced disease.

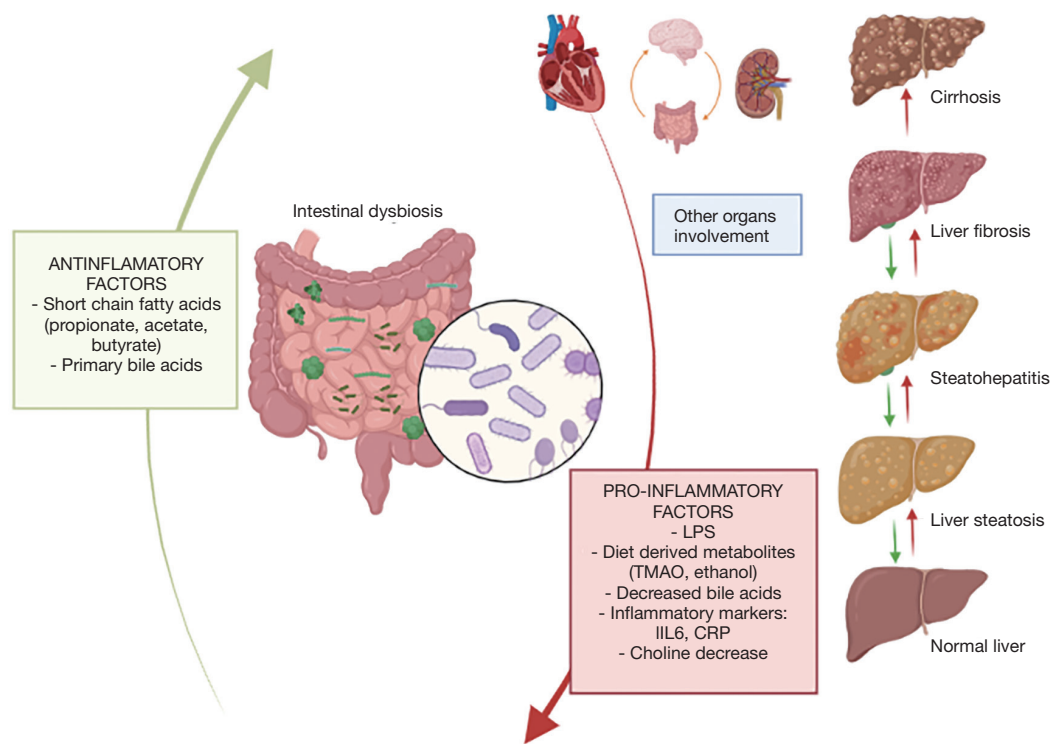
### Autoimmune diseases

#### Autoimmune hepatitis (AIH)

Some studies have characterized the microbiome of patients who had not received steroid treatment for AIH. Wei *et al.* found that these patients had a depletion of obligate anaerobes such as *Faecalibacterium*, as well as the expansion of *Veillonella*. *Veillonella disbar* was linked to the severity of the disease and inflammation of the liver (45). A disease-specific decrease in the relative abundance of *Bifidobacterium* in patients with AIH have been described. In other study by Liwinski *et al.*, found that the lack of *Bifidobacterium* was associated with failure to achieve AIH remission and with an increased disease activity (46).

#### Primary biliary cholangitis (PBC)

PBC is the most common autoimmune liver disease, occurring approximately 0.1% of women in their 40s. It is characterized by the presence of antimicrobial antibodies and the destruction of the intrahepatic biliary ducts, allowing fibrosis and potentially cirrhosis. The microbiota plays an important role, a decrease in genera such as *Faecalibacterium*, *Bacteroides*, *Sutterella* and *Oscillospira* spp has been described, as well as an increase



**Figure 2** Relationship between the gut microbiota and the progression of metabolic fatty liver disease (39-42). This figure illustrates how gut-derived metabolites are related to the development and progression of MAFLD, fibrosis, and cirrhosis. Products such as ethanol, lactate and TMAO can accelerate the progression of MAFLD (TMAOs induce a decrease in bile acid reserve, affecting FX receptor signaling). On the other hand, SCFAs may have anti-inflammatory properties, which could prevent the progression of MAFLD. MAFLD, metabolic associated fatty liver disease; TMAO, trimethyl N oxide; IL 6, interleukin 6; CRP, C-reactive protein; ALD, alcoholic liver disease; SCFA, short-chain fatty acids.

in Enterobacteriaceae such as *E. coli*, *K. pneumonia* and *E. cloacae* (47). Lipoteichoic acid, a cell wall component of gram-positive bacteria, was augmented in destroyed bile ducts of liver samples and in serum of PBC patients compared to patients with hepatitis C (48).

### Primary sclerosing cholangitis (PSC)

PSC is a cholestatic liver disease, characterized by inflammation and stenosis of the bile ducts. Recent studies have described the relationship of this disease with the gut-liver axis, with a decreased microbiota diversity in patients with PSC. Characterization of the fecal microbiota in adult PSC has shown elevated levels of certain species, such as *Veillonella*, *Fusobacterium*, *Streptococcus parasanguinis*, *Enterococcus faecium*, *E. coli*, *Faecalibacterium*, *Ruminococcus* and *Roseburia*. There is also a reduction in short-chain fatty acid-producing bacteria, such as Firmicutes, *Faecalibacterium*, and *Coprococcus*, as well as the reduction

of *Anaerostipes hadrus*, *Proteobacteroides distasonis* and *Blautia obeum* (49-51). *Veillonella* has also been associated with other chronic inflammatory disorders. It appears that the abundance of *Veillonella* species and the over-representation of the genus *Enterococcus* exhibit a signature in PSC patients. This suggests that *Veillonella* and *Streptococcus* species might be related to the immune modulation and the activation of inflammatory pathways in PSC (51). Interestingly, the microbiota in PSC patients seems to be similar, whether or not they have inflammatory bowel disease (IBD); suggesting that PSC might drive microbiota alterations (52).

### End stage CLD and intestinal microbiome

Cirrhosis, the final stage of liver fibrosis, is classified into compensated or decompensated states. The main complications such as hepatic encephalopathy and



spontaneous bacterial peritonitis are related to alterations in the gut-liver axis (19). There are changes in the composition of the microbiota between healthy control and those with liver cirrhosis. The main changes observed are the reduction in Lachnospiraceae and Ruminococcaceae, bacteria that are associated with the production of SCFAs and the formation of primary and secondary bile acids. An increase in pathogens such as Enterobacteriaceae that produce endotoxins and lipopolysaccharides, has also been observed, reducing SCFAs, causing an increased intestinal permeability and promoting the passage of LPS and bacterial products to the liver; causing hepatic and systemic inflammation (53). The increase of bacteria of oral origin, such as *Veillonella parvula* and *Streptococcus salivarius*, has been shown in cirrhotic patients who received proton pump inhibitors (PPIs), increasing intestinal permeability and promoting cirrhosis progression (54). Other studies have shown an increase in the microbiota of the oral cavity such as Veillonellaceae, Porphyromonadaceae and Streptococcaceae, later it was reported that this is an epiphenomenon due to the use of PPIs, which decreases when they are suspended (55). Other oral-derived bacteria *Rothia*, Streptococcaceae and Veillonellaceae have been associated with cirrhosis complications and progression (56,57). Changes in the concentration of colonic fungi (*Candida spp*) have been described in patients with advanced CLD. This is compounded using broad-spectrum antibiotics. These findings indicate that cirrhosis is a systemic disease that worsens with dysbiosis. Importantly, the concentration of potentially pathogenic bacteria, such as Enterobacteriaceae and Streptococcaceae, associated with the reduction of beneficial populations such as Lachnospiraceae could accelerate the progression and affect the prognosis of these patients. Intestinal dysbiosis seem to be more severe the more advanced the hepatic decompensation is (36).

### **Cirrhosis complications and microbiome**

#### ***Hepatic encephalopathy and microbiota***

Hepatic encephalopathy is a complication of cirrhosis, it is a syndrome characterized by neurocognitive deterioration, where the pathophysiological substrate is hyperammonemia produced mainly by Enterobacteria (19). Hepatic encephalopathy is a neurological complication that occurs in individuals with CLDs typically divided into three types [type A resulting from acute hepatic failure (ALF), type B resulting from portosystemic bypass or shunting, and type C resulting from cirrhosis]. Ammonia has been known to play a central role in the pathogenesis of HE. Urease is a bacterial

enzyme that catalyzes the hydrolysis of urea to carbamate and ammonia. Compared to healthy controls, intestinal microbiota on patients with cirrhosis have an abundance of 75,245 genes according to quantitative metagenomics. The genus Bacteroidetes decreases according with a decrease in liver function. Some intestinal microbiota have been correlated with the pathological mechanisms, processes and outcomes of HE. The translocation of *Methylobacterium extorquens* and *Stenotrophomonas pavanii* into the peripheral blood system enhances the risk of HE.

#### ***Effects of clinical treatment on the intestinal metabolome in hepatic encephalopathy***

Various drugs are used to lower blood ammonia levels. Lactulose is the most widely used ammonia-reducing drug. It is a laxative drug, nonabsorbable disaccharide. It also inhibits intestinal bacterial overgrowth, translocation and intestinal resistance, in patients with liver cirrhosis, clinical doses of lactulose promote the growth of beneficial bacteria, such as Lactobacillus and Bifidobacterium, increase the abundance of hydrogen-producing bacteria Rikenellaceae and Prevotellaceae, and mucin-degrading bacteria Akkermansia and Helicobacter; and decrease the abundance of harmful bacteria Desulfovibrionaceae (58,59). Intestinal antibiotics have been tested for the treatment of HE. Among them the most widely used is Rifaximin is a non-systemic antibiotic approved for the treatment of HE. It has bactericidal and bacteriostatic activity *in vitro* against aerobic and anaerobic Gram-positive and negative species, and can also reduce bacterial virulence and translocation, it also inhibits bacterial adherence to the intestinal mucosal, with a decrease in Roseburia, Haemophilus, Veillonella and Streptococcus and increase in Lactobacilli after 10 days of rifaximin administration, this is in line with the evidence that rifaximin is able to promote the growth of beneficial bacteria (60). Other antibiotics such as neomycin are not recommended because of their side effects (58). Probiotics (including *Bifidobacterium longum*, *Lactobacillus paracasei*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Bifidobacterium breve*, *Lactobacillus plantarum*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*) have several mechanisms that may be involved in hepatic encephalopathy improvement and may include: modulation of the gut microbiota, reduce total ammonia in portal blood by decreasing bacterial urease activity, decrease ammonia absorption by lowering pH, decrease intestinal permeability, and improve nutritional status of gut epithelium, in addition, probiotics can stimulate the production of SFCAs by increasing the abundance of multiple bacteria, including

*Syntrophococcus sucromutans*, *Calibacterium prausnitzii*, and *Alistipes shabii* (61,62).

#### **HCC and microbiota**

The persistent inflammation and liver fibrosis associated with CLD described above also tend to favor the accumulation of genetic and epigenetic changes, such as mutations in the telomerase reverse transcriptase promoter, tumor protein p53 or signaling genes, which lead to HCC development. More recent studies have delineated that the gut microbiota in NAFLD-related HCC animal models has increased Bifidobacterium and a group of organisms in the Clostridiales order, formerly known as the “Clostridium cluster XVIII.” Both groups are involved in bile acids (BA) modification and are involved in the conversion of primary BAs to secondary BAs, such as deoxycholic acid (DCA) (17). No differences have been found in the intestinal microbiota of patients who developed or had previous HCC; however, specific microbiota traits have been described in patients with HCC. In HCC NAFLD patients, a higher concentration of Enterococcus, Bacteroides, Clostridium, Paraprevotella and Ruminococcaceae, and a reduction of Bifidobacterium, Alphaproteobacteria and Akkermansia have been described (57,60). Streptococcus and Enterococcus have been reported to be related to the progression of cirrhosis and the development of HCC. (60) Lapidot *et al.* demonstrated that NAFLD patients who developed HCC had increased concentrations of Akkermansia (63). It has also been reported that HCC patients have a reduction in bacteria that produce SFCAs as Roseburia, Odoribacter, *Clostridium sensu stricto* (64). The *Clostridial Anaerotruncus* and *Clostridium sensu strictus* taxa have also been reported to be associated with the absence of HCC. Yoshimoto *et al.* found an association between HCC and the predominantly Clostridium XI and XIVa clusters (65).

#### **Acute on chronic liver failure and microbiome (ACLF)**

Acute on chronic liver failure is a clinical entity that occurs in patients with CLD with a triggering event that decompensates it. It is also characterized by multiple organ failure, including hepatic encephalopathy, has a rapid progression, a poor prognosis and a high mortality. The microbiota presents classic alterations such as the increase in Streptococcaceae, Enterobacteriaceae, Alcaligenaceae and Porphyromonadaceae, Lachnospiraceae, and a reduction in Bacteroidetes, Proteobacteria, Firmicutes (66). There is evidence that translocation of components of the gut microbiota (LPS), facilitated by different pathogenic

mechanisms (increased intestinal permeability and portal hypertension), is an important driver of decompensation by the induction of systemic inflammation, and thereby ACLF, as shown in *Table 3* (49,67-69).

#### **Facts and fictions about gut microbiota**

The gut is called “the second brain” because it is wired similarly to the brain, with neurons and neurotransmitters. In many studies, the relationship between the microbiota and multiple diseases has been demonstrated, as well as its participation in their pathophysiology, such as cancer, metabolic disorders, autoimmune inflammatory processes and neuropsychiatric diseases (70,71). Current data on the role of the gut microbiota in CLD is constantly evolving and is not fully understood. The gut microbiota has been shown to play a key role in promoting health. Commensal bacteria produce important SCFAs that stimulate the regeneration of enterocytes, they also promote the preservation of the TJ proteins, preserving the integrity of the intestinal barrier. When the balance of commensal bacteria is disturbed, bacteria such as Proteobacteria increases, promoting the secretion of intestinal inflammatory cytokines. The increased intestinal permeability and dysbiosis cause the continuous passage of PAMPS, such as LPS, bacteria and inflammatory cytokines to the liver, activating Kupfer Cells TLR that activates the innate immune response. In ALD, beyond these facts, acetaldehyde, a metabolite of alcohol metabolism, has been shown to disrupt TJ proteins, reduce intestinal motility, and cause intestinal bacterial overgrowth with higher proportions of *Bifidobacterium*, *Streptococci*, and *Enterobacteria*. *Enterococcus faecalis* in ALD is highly correlated with the severity of the disease. Similar facts in intestinal permeability have been shown in patients with MAFLD. MAFLD patients have an increase in *Escherichia coli* associated with susceptibility to leaky gut. In autoimmune liver disease, there has also been demonstrated comparable findings of dysbiosis and leaky gut. In PSC, *Klebsiella pneumonia* have been shown to alter intestinal integrity inducing pore formation in the epithelial layer. PSC patients also have increase concentration of lactobacillus gasseri that induce inflammatory injury (69). In autoimmune hepatitis, there is an increase in *Veillonella dispar*, which has been related to the severity of the disease. In PBC an increase in *Klebsiella pneumonia* in stool has been documented, producing microbiome alterations and increasing intestinal permeability (45). In cirrhosis, it has been described several characteristics

**Table 3** Liver diseases and alterations in the microbiota (49,67-69)

Liver disease	Intestinal microbiome
MAFLD	Increase: Bacteroidetes, <i>Clostridium coccoides</i> , Bacteroides, <i>E. coli</i> , <i>Bacteroides vulgatus</i> , Acidaminococcus, Streptococcus, Gallibacterium, enterobacteriaceae, <i>Ruminococcaceae</i> ( <i>Ruminococcus gnavus</i> ), Enterococcus, Phascolarctobacterium, Blautia, <i>Veillonella parvula</i> , <i>Veillonella atypica</i> . Decrease: Firmicutes, Clostridiales, Faecalibacterium, Prevotella, <i>Eubacterium eligens</i> , <i>E. rectale</i> , <i>Faecalibacterium prausnitzii</i> , Bifidobacterium, Blautia
ALD	Increase: Enterobacteriaceae, including the predominant species <i>Escherichia coli</i> , Bacteroidaceae. Decrease: <i>Lachnospiraceae</i> , <i>Lactobacillus spp</i> , <i>Bifidobacterium spp</i> , <i>Ruminococcaceae</i> , Clostridiales XIV
Autoimmune (PSC, PBC, AIH)	PSC Increase: Bacilli, Pseudomonas, Streptococcus, <i>E. coli</i> , Barnesiellaceae, Blautia, <i>Ruminococcus obeum</i> , Veillonella, Lactobacillus. Decrease: <i>Lachnospiraceae</i> , Prevotellaceae, Paraprevotellaceae, Bacteroides, Faecalibacterium. PBC Increase: Enterobacteriaceae such as <i>E. coli</i> , <i>K. pneumoniae</i> , and <i>E. cloacae</i> . Decrease: Faecalibacterium, Bacteroides, Sutterella and <i>Oscillospira spp</i> . AIH Increase: Veillonella Decrease: anaerobes such as Faecalibacterium, Bifidobacterium
End stage chronic liver disease	Increase: Veillonillaceae, Porphyromonadaceae, Streptococcaceae, Enterobacteriaceae, Candida Decrease: <i>Lachnospiraceae</i> and <i>Ruminococcaceae</i>
Hepatic encephalopathy	Increase: Enterobacterias Decrease: Bacteroides
Hepatocellular carcinoma	Increase: Bacteroides, Oscillospira, Enterococcus, acteroides, Clostridium, Paraprevotella and <i>Ruminococcaceae</i> Decrease: Clostridium XI y XIVA, Bifidobacterium, Alphaproteobacteria and Akkermansia
ACLF	Increase: Streptococcaceae, Enterobacteriaceae, Alcaligenaceae y Porphyromonadaceae, <i>Lachnospiraceae</i> Decrease: Bacteroidetes, Proteobacteria, Firmicutes

MAFLD, metabolic associated fatty liver disease; ALD, alcoholic liver disease; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; ACLF, acute on chronic liver failure.

in gut microbiota that predispose to the development of cirrhosis complications, among them Lactobacillae enrichment have been found to be associated with enhance neuroinflammation and ammonia levels (72). Another important fact is the relationship of gut microbiota and BA. Alteration in microbiota alter the balance of primary and secondary BA, provoking a disturbance in FXR activation, BA enterohepatic circulation and BA production, causing an increase in metabolic stress and host immune response activation (45). For trying to explain all these effects of gut microbiota within the host, several criteria have been proposed; among them, Hill's inference criteria that are applicable to several pathologies related to the intestinal microbiota and Koch's criteria. Koch's Criteria explain that commensal bacteria may colonize a host this supports the fact of the effectiveness of fecal microbiota transplant for the treatment of several diseases (73,74).

In the other hand, a lot of facts have not yet been proven or remain unknown; among them, the role of probiotic treatment in liver diseases, which could improve dysbiosis and reduce intestinal permeability (75). We are far away for fully understanding the effect of microbiota in host metabolism and liver diseases, therefore additional knowledge of this important field will help us to better understand liver disease development and progression, to propose a better target treatment to our patients. As shown in *Table 4*.

## Conclusions

The gut microbiota plays a crucial role in the pathogenesis and progression of liver diseases. Microbiota alterations have been characterized in several CLD s and, although it is not fully understood, the effect of dysbiosis on the progression of CLD has been described, providing a strong

**Table 4** Facts and fictions about microbiota stratified by the strength of the evidence (75-80)

## Strong evidence

1. Colonization by the microbiota of all surfaces begins from birth
2. Environmental factors are the most important for the differentiation of the microbiota
3. There is variability in the conformation of the microbiota between individuals
4. The microbiota plays an important role in the pathogenesis of diseases such as irritable bowel syndrome, ulcerative colitis, Crohn's disease, liver cirrhosis
5. The microbiota has metabolic, inflammatory and endocrinological functions

## Medium evidence

1. The microbiota can also influence and change the effectivity of vaccines and it can impact the immune response
2. There are different hypotheses of the influence of the intestinal microbiota on colorectal cancer, impacting on its development and treatment
3. Probiotics may modify Composition and restore "Healthy Microbiota"

## Weak evidence

1. It is controversial whether dysbiosis is the etiological factor of various diseases or is only a cofactor
2. There is not enough information on the role played by the rest of the components of the microbiota on health (fungi, viruses)

rational to deeply explore the importance of the alteration of the microbiota in the development and progression of CLD. Microbiota taxa could represent important biomarkers and could become important therapeutic targets of patients with CLD.

There is still much to investigate regarding the different molecular mechanisms that link the intestinal microbiota and its complex microbiota-liver-brain axis, this may lead to the development of different treatments for liver diseases where it has been documented that the microbiota plays an important role.

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