

Review

# Viral Liver Disease and Intestinal Gut–Liver Axis

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**Abstract:** The intestinal microbiota is closely related to liver diseases via the intestinal barrier and bile secretion to the gut. Impairment of the barrier can translocate microbes or their components to the liver where they can contribute to liver damage and fibrosis. The components of the barrier are discussed in this review along with the other elements of the so-called gut–liver axis. This bidirectional relation has been widely studied in alcoholic and non-alcoholic liver disease. However, the involvement of microbiota in the pathogenesis and treatment of viral liver diseases have not been extensively studied, and controversial data have been published. Therefore, we reviewed data regarding the integrity and function of the intestinal barrier and the changes of the intestinal microbioma that contribute to progression of Hepatitis B (HBV) and Hepatitis C (HCV) infection. Their consequences, such as cirrhosis and hepatic encephalopathy, were also discussed in connection with therapeutic interventions such as the effects of antiviral eradication and the use of probiotics that may influence the outcome of liver disease. Profound alterations of the microbioma with significant reduction in microbial diversity and changes in the abundance of both beneficial and pathogenic bacteria were found.

**Keywords:** gut–liver axis; intestinal barrier; chronic viral hepatitis; microbiota; dysbiosis



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## 1. Introduction

A connection between the intestine and the liver was already postulated approximately two thousand years ago when the Greek-Roman doctor Galen suggested a connection between the gut and the liver [1].

In modern medicine, the clustering of microorganisms living in the same environment has been defined as microbiota, while the term microbiome applies to the collective genomes of the microbes [2,3]. Microbiota are composed of bacteria, archaea, protozoans, fungi, and viruses [4]. Interestingly, every human being has their unique composition of gut microbiota properly defined as the “microbial fingerprint” [5].

The bacterial component of the microbiota is classified into 12 different phyla and 93.5% of the total belongs to *Proteobacteria*, the Gram positive *Firmicutes*, *Actinobacteria*, and the Gram negative *Bacteroidetes*. *Bacteroides* and *Prevotella* are the main genera of *Bacteroidetes*. *Clostridium*, *Blautia*, *Enterococcus*, *Faecalibacterium*, *Eubacterium*, *Roseburium*, *Ruminococcus*, *Streptococcus*, and *Lactobacillus* are the most prevalent genera of *Firmicutes*. *Actinobacteria* include *Bifidobacteria*, *Atopobium*, and *Collinsella*, while *Proteobacteria* are mainly composed of *Enterobacteriaceae* such as *Escherichia* and *Klebsiella*. *Akkermansia muciniphila* is the only species of *Verrucomicrobia* found in the human gut [6–8]. *Archaea* are predominated by *Methanobrevibacter* species. Viruses and bacteriophages are also colonizing the gut in considerable quantities [9].

*Firmicutes* and *Actinobacteria* predominate among luminal bacteria populations, while *Proteobacteria* are abundant among mucosal populations [10]. Early in the life of humans, there is a restricted diversity of the microbiota which is mostly composed of *Actinobacteria*

and *Proteobacteria*. Diversity and variability are increasing with age and the species of *Bacteroides*, *Clostridium*, and *Escherichia coli* predominate in the intestinal flora in individuals over 65 years of age [11–13]. The gut microbiome is also variable among different ethnic groups [14–16] and between rural and urbanized populations of the same ethnicity [15–18]. Microbiota also differ between countries and continents [14,15,19].

Fungal species are also found in the gut including *Candida*, *Saccharomyces*, *Aspergillus*, *Penicillium*, *Rhodotorula*, *Trametes*, *Pleospora*, *Sclerotinia*, *Bullera*, and *Galactomyces* [20].

The human intestinal microbiota is now considered as a significant superorganism [21], colonized by approximately one-hundred trillion bacteria comprising nearly 40,000 types of microbes [22–25] most of which cannot be cultured, and 200–300 fungal species [26–28]. Microbial cells in the body are 10- to 100-fold higher than human cells [29,30]. In all, the microbiota weights approximately 1–2 kg in the adult, while the genetic material exceeds that of the human by about 100 times indicating its significance in human homeostasis [31,32].

There are several pathways of communication between microbes and the human host. This is achieved through different microbial components and products such as lipopolysaccharides (LPS), bacterial DNA, flagellin, short-chain fatty acids (SCFAs), tryptophan (Trp), and secondary bile acids (BAs) [33]. All these are recognized by pattern recognition receptors, mainly the Toll-like receptors (TLRs) family.

These pathways have been recently studied in connection with alcoholic or metabolic liver disease, but viral hepatitis and its consequences have not studied in depth. The purpose of this review, therefore, is to present the current data on the interplay between the intestinal microflora and chronic viral disease and the therapeutic implications of the manipulation of the gut microbiota.

## 2. The Gut–Liver Axis

The gut–liver axis is the mutual interaction between the gut microbiota and the liver. The portal vein transports gut produced components directly to the liver, and the liver provides the intestine with bile components including a wealth of antibodies [34]. A critical element of this mutual communication is the intestinal permeability. Bacterial products cross the intestinal barrier and modify the gut-associated lymphatic tissue (GALT) to release cytokines and chemokines along with other bacterial metabolites such as trimethylamine, and ethanol. A second barrier, the gut–vascular barrier (GVB), is the molecular sieve of components entering the portal-venous circulation to directly reach the liver [35–37].

The intestinal mucosal barrier is a complex functional structure consisting of three elements (a) the physical element comprised of several types of cells sealed by the tight intercellular junctions, (b) the gut-associated lymphoid tissue comprised of several immune cells in concert with the Peyer’s cells and mesenteric lymph nodes, and (c) the mucus layer secreted by the goblet cells that also contains immunoglobulin A (IgA) and antimicrobial products [38,39]. The function of the intestinal barrier is to maintain the tolerance to commensal organisms and food antigens and to mount a protective immune reaction to microbial pathogens and/or to microbial components defined as pathogen-associated molecular patterns (PAMPs) [40].

### 2.1. Physical Elements of the Intestinal Barrier

The intestinal barrier is a single layer of cells comprised of enterocytes, goblet cells, Tuft cells and enterochromaffin cells [41]. A physical barrier is provided by the cellular monolayer and the tight junctions, and an electrical barrier is operational as the negatively charged brush border repels the negative charge of the microbiota. In addition, many hydrophilic molecules are denied passage by the hydrophobic nature of cell membranes of intestinal cells. The integrity of the epithelial barrier is further accomplished by an intercellular seal comprised—from the apex of the cell to the base—of tight junctions (TJs, zonula occludens), the adherens junction (AJ, zonula adherens), and the desmosome (macula adherens) [41,42]. TJs consist of more than 50 proteins. Membrane-associated scaffolding proteins such as zonula occludens 1, 2, and 3 anchor TJ to the actin cytoskeleton [43,44].

They include tight junction-associated MARVEL proteins (TAMPs), claudins, and junctional adhesion molecules (JAMs) [43,45]. The function of TAMPs, such as occludin, is not completely clarified as TJs are formed even in the absence of occludin [45]. More than 27 claudin family members have been described [46]. JAMs, on the other hand, are related to signaling pathways of cell polarity and regulate permeability via non-selective pathways [47–49].

As mentioned before, there is a second physical barrier, the gut–vascular barrier that also contains TJs and AJs. This barrier prevents bacterial and antigen translocation from entering the portal circulation and reaching the liver due to the presence of the plasmalemma vesicle-associated protein-1. Its function is dependent on the Wnt/ $\beta$ -catenin signaling pathway. *Salmonella typhimurium* can cross this barrier by interfering with Wnt/ $\beta$ -catenin that controls AJ functionality via E-cadherin/ $\beta$ -catenin [50,51]. It should be noted that Hepatitis B virus also affects the Wnt/ $\beta$ -catenin signaling [52].

## 2.2. Control of the Microbiota by the Gut-Associated Lymphoid Tissue

Several immune cells contribute to the intestinal barrier. Dendritic cells, various subgroups of lymphoid cells, and macrophages protect from pathogens and provide the necessary tolerance to ingested food antigens and commensal bacteria [53]. Immune cells are located either in the lamina propria or within the epithelium. Intraepithelial cells include  $\alpha\beta$  and  $\gamma\delta$  T lymphocytes and mononuclear phagocytes [54–56]. Intraepithelial lymphocytes are cytolytic and are activated by epithelial cell cytokines [57]. Intraepithelial phagocytes are critical for tolerance development. Their luminal protrusions sense bacterial and food components and present their peptides into the lamina propria dendritic cells [58]. Immunocytes of the lamina propria are the next line of protection. CD4+ T lymphocytes, innate immunity associated NKT cells, and mucosal associated invariant T cells (MAIT cells) are highly specialized for particular antigens. NKT cells recognize lipids [59], while MAIT cells recognize metabolites of vitamin B2 [60,61]. CD4+ T cells are mostly Th17 cells that are induced after adhesion of filamentous bacteria to the intestinal epithelium [62,63], and T regulatory cells [64]. The production of IL-22 by Th17 cells improves the integrity of the tight junctions. Conversely, production of IL-17 is pro-inflammatory and pro-fibrotic [65]. Interactions between the host and the microbiota are mediated by soluble factors called postbiotics [66,67]. Intestinal microbes produce during the degradation of dietary fibers short chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, which are the main postbiotics. SCFAs are consumed by other butyrate-producing microorganisms, such as *Roseburia*, *Faecalibacterium*, and *Eubacterium* [68]. SCFAs directly strengthen tight junctions [69,70]. They also stimulate mucin production and intestinal motility [66]. SCFAs also sensitize intestinal epithelial cells (IEC) to bacterial products [71]. They also regulate immunity in the GALT as they inhibit macrophage and dendritic cell activation and shape the T helper cell repertoire [72–74] controlling the differentiation of T regulatory cells [75]. *Bifidobacteria* are examples of protective bacteria that produce SCFAs leading to decreased production of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 by macrophages while reinforcing production of IL-10 [76,77]. Conversely, bacteria of the *Enterobacteriaceae* family such as *Klebsiella*, *Escherichia coli*, *Proteus*, and *Enterobacter* produce ethanol and promote liver damage [78]. They also release large amounts of lipopolysaccharide (LPS) in the intestinal lumen that favor the production of pro-inflammatory cytokines [79], and increase intestinal permeability and the translocation of bacteria [80].

Commensal bacteria also strengthen the barrier through their interaction with Toll-like receptor (TLRs) [81] and the production of mediators that can affect the binding proteins [82,83]. Isoforms of protein kinase C are phosphorylated after activation of TLR2 leading to up-regulated expression of zona occludens and the sealing of tight junctions [82]. On the other hand, the expression of occludin is down-regulated after activation of TLR4 increasing intestinal permeability [83]. *Escherichia coli* and *Clostridia difficile* are examples of bacteria that can affect the binding proteins and open the paracellular routes [84]. Humans express ten TLRs [85] responding to viral and bacterial proteins or endogenous ligands without infection [86]. Kupffer cells, the main cells responding to TLRs ligands,

express all TLRs except TLR5 [87]. Hepatocytes, biliary endothelial cells, hepatic stellate cells (HSCs), and sinusoidal epithelial cells also express TLRs, but only HSCs express all nine TLRs [88,89]. The production of inflammatory cytokines, chemokines, and reactive oxygen species by the Kupffer cells after TLRs activation, lead to liver damage [90] and the activation of both the innate and adaptive immune immunity [91,92]. Ligands bind to all TLRs except TLR3 and activate a signal pathway operated by the myeloid differentiation factor 88 (MyD88) [93,94] that in turn activates nuclear factor-kappa B (NF- $\kappa$ B) and promotes the transcription of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 [85]. More specifically, activation of TLR4 and TLR9 releases IL-12 and pro-inflammatory cytokines [95], while TLR4 activation may also induce the release of IL-23 that favors the survival of pro-inflammatory Th 17 lymphocytes [96]. On the other hand, activation of TLR2 releases the anti-inflammatory IL-10 and IL-13 [97]. LPS from Gram-negative bacteria activates TLR4 [85,98], while unmethylated CpG bacterial and viral sequences activate TLR9 [99]. TLR2 is activated by ligands of the HCV virus [86,100,101]. Endotoxin-mediated activation of TLR4, TLR9, and macrophage TLR2 activation by endotoxin is the primary driver of the development of liver fibrosis [102–105]. TLR4 signaling induces fibrosis by reducing the BMP and activin membrane-bound inhibitor homologue (BAMBI) which is a decoy receptor for TGF- $\beta$  in hepatic stellate cells [106]. TLRs activation also increase the expression of the major histocompatibility complex on antigen presenting cells [107].

Intestinal epithelial cells (IECs) are also involved in intestinal immunity as they are exposed to a wealth of antigens acting as sensors of the microbiome through the pattern recognition receptor families such as the nucleotide-binding oligomerization domain-like receptors (NODs), TLRs, and the aryl hydrocarbon receptor (AhR). IECs, unlike immune cells, produce through TLR4 and AhR signaling interleukin-10 (IL-10), leading to tolerance to commensal bacteria. Commensal stimulation of IECs also promotes tolerance of dendritic cells and macrophages through the production of transforming growth factor beta (TGF- $\beta$ ), IL-10, and retinoic acid (RA) [40,108]. Interestingly, only limited species such as *Peptostreptococcus russellii* and *Lactobacillus* produce AhR ligands [109]. *Lactobacilli* species can convert Trp into indole-3-aldehyde, a ligand for AhR leading to the production of IL-22 [110].

Detailed description of the interaction of HCV, HBV, and the TLRs have been published [111,112].

### 2.3. Stratification of the Microbiota by Mucus

The mucus separates the microbiota from the intestinal cells and inhibits an excessive inflammatory reaction. Very few species, such as the *filamentous bacteria*, present in early life [113], can cross the mucus directly interacting with the epithelial cells [62]. All other bacteria indirectly interact with the host through their metabolic products [66,114,115]. Intestinal mucus has two layers: the almost sterile inner layer attached to the epithelium, and the outer layer colonized by bacteria. Mucus is thicker in the terminal ileum and large bowel [116,117]. Secreted mucins (MUCs), such as MUC2 and transmembrane MUCs, comprise the inner and outer mucous layers [118]. Bacteria can attach to mucus through the mucin-immunoglobulin A interactions [119]. The composition of the mucus is determined by the diversity of microbiota [120] because goblet cells sense the presence of different bacterial products. This is probably due to the capacity of the so-called sentinel goblet cells to act as sensors for the presence of different bacterial products and to modify MUC2 mucin secretion after activation of the Nlrp6 inflammasome [121]. It should be noted that several bacteria, such as *Akkermansia muciniphila*, can degrade mucins and use them as a source of nutrients [122].

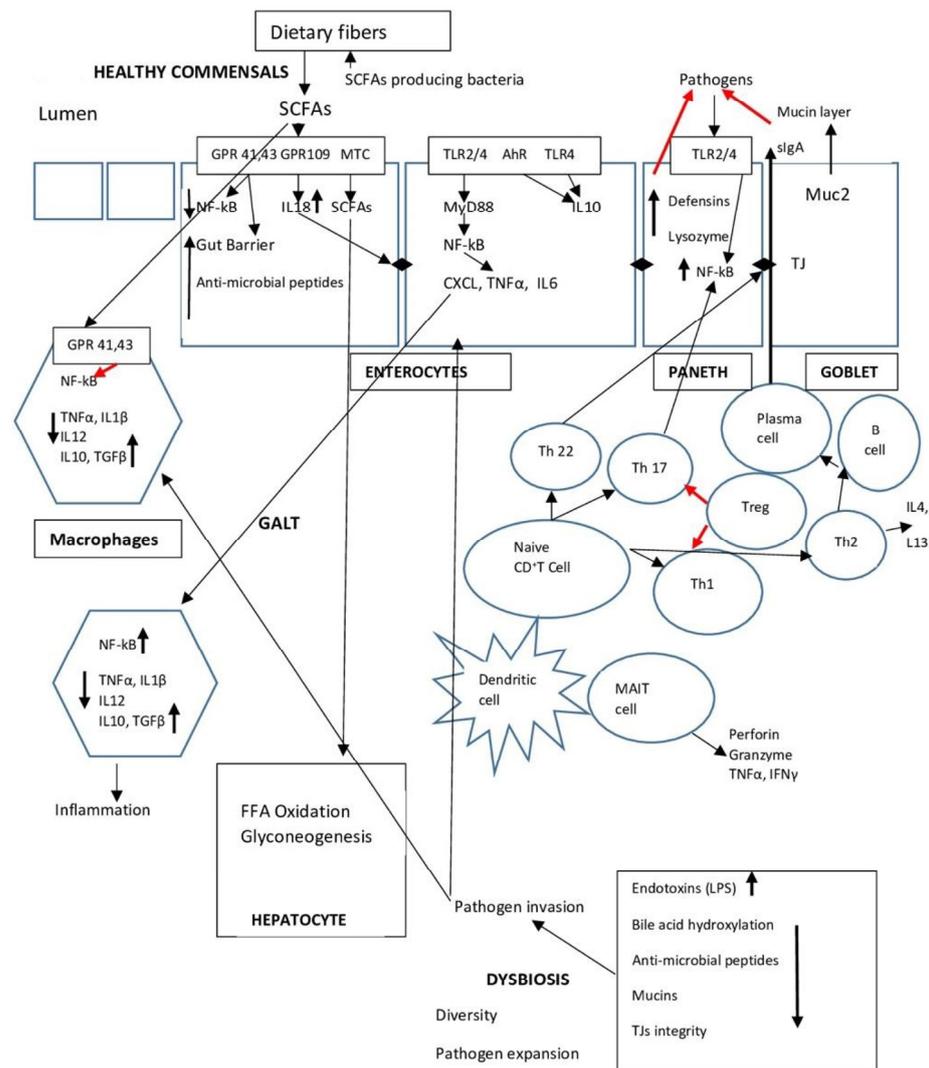
The intestinal mucus layers increase their defenses by antibacterial lectins, such as the regenerating islet-derived protein III $\gamma$  (REG3G), which are secreted by the Paneth cells to fight bacteria present in the mucosal lining [123–125]. In addition, plasma cells can secrete immunoglobulins A (sIgAs) which is transported to the lumen and neutralize microbial pathogens [126]. IgA may be used by commensal microbes, such as *Bacteroides*

*fragilis*, to facilitate mucus attachment [127]. Additionally, sIgAs neutralize bacterial toxins as well [128,129]. The large diversity of antimicrobial peptides inhibits bacteria to develop resistance to these proteins [130].

Apart from intestinal inflammation, the most important driver of dysregulated barrier permeability is intestinal dysbiosis [131,132]. The major unsolved problem with dysbiosis is whether it is the cause or the effect of the disease. The main promoter of dysbiosis is the use of antibiotics leading to their association with several autoimmune diseases [133–136]. Dysbiosis may result from either a reduction of beneficial microorganisms or the predominance of pathogens and the alteration of the total microbial diversity [137]. Intestinal dysbiosis usually leads to tight junctions weakening and increased translocation of microbes or microbial elements such as LPS, DNA, and  $\beta$ -glucan from fungi. They are collectively designated as microbial-associated molecular patterns (MAMPs) or pathogen-associated molecular patterns (PAMPs). MAMPs and PAMPs can activate Kupffer and hepatic stellate cells that ultimately lead to liver damage and fibrosis [106,138–140].

The communication between the gut and the liver is achieved through the biliary tract and the portal vein. Liver produced mediators such as bile acids influence the gut microbiota and intestinal permeability, while intestinal products are involved in bile acid synthesis and glucose and lipid metabolism in the liver [141,142]. Translocation of gut bacteria or bacterial components to the liver, mesenteric lymph nodes, and other extra-intestinal sites is the result of tight junction abnormalities [106,143,144]. Lactate, which is produced by bacterial carbohydrate fermentation, reduces barrier permeability before its own fermentation to butyrate by intestinal flora [145]. Harmful bacterial products, such as LPS and unmethylated CpG, are then delivered to the liver and activate TLRs as mentioned before [85].

An important mechanism in the bidirectional communication between the liver and the intestine is the enterohepatic circulation of bile acids (BAs) [146]. Primary BAs, such as cholic acid (CA) and chenodeoxycholic acid (CDCA), are involved in enterohepatic circulation after their secretion by the hepatocytes. They are transported to the intestinal lumen as glycine or taurine conjugates [147]. In the lumen, the bacterial enzyme bile salt hydrolase (BSH) acts on BSH is produced by both Gram-positive and Gram-negative bacteria in the gut such as *Bacteroides*, *Clostridium*, *Lactobacillus*, *Bifidobacterium*, and *Listeria* [148]. Luminal bile acids are re-absorbed in the terminal ileum by the apical sodium-dependent bile acid transporter (ASBT) or passively cross the epithelium in the colon [36]. Secondary BAs may increase intestinal permeability affecting the stability of cellular membranes [149]. Gut bacteria also control the synthesis of BAs in the liver through the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (GPBAR1, also known as TGR5) [150]. FXR is a transcriptional nuclear receptor mostly expressed in the liver, ileum, and kidneys. It is involved in lipid and glucose metabolism [151,152]. BAs bind to FXR of the enterocytes, inducing the transcription the fibroblast growth factor 19 (FGF19). FGF19 is consequently transported to the liver via the portal vein and binds to FGF receptor 4 on hepatocytes. This binding inhibits the enzyme cholesterol 7 $\alpha$ -monooxygenase (CYP7A1) and reduces the de novo BA synthesis in hepatocytes [153–155]. In addition, binding of BA to FXR induces the production of antimicrobial peptides, such as angiogenin 1 and RNase family member 4, which restrict gut microbial overgrowth and intestinal barrier dysfunction [156,157]. FXR engagement can therefore preserve the epithelial barrier [158] and repair damage of the gut vascular barrier [159]. Additionally, BAs binding to TGR5 on the enterocyte membrane mediates host energy expenditure [160,161] and glucose homeostasis [162]. Figure 1 graphically depicts the complex interrelations as described above.



**Figure 1.** Summarizes the main points of the interplay between microbiota, the intestinal barrier, and the gut immune system (GALT).

### 3. HBV Infection and Intestinal Microbiota

There are approximately 296 million people with chronic HBV infection worldwide, while 887,000 people die each year from complications of chronic HBV infection [163,164].

#### 3.1. HBV and Intestinal Dysbiosis

HBV infection may be associated with intestinal dysbiosis [165] as demonstrated from animal experiments and clinical data. Thus, the ratio of *Bacteroidetes* and *Firmicutes* was stable in control mice, but it was significantly different in mice with HBV infection. Interestingly, differences were observed in *Lactobacillus* and *Bifidobacterium* between acute or chronic HBV infection [166]. In another experiment, decreased *Blautia* and *Clostridium* in HBV-infected mice were negatively correlated and increased *Butyricoccus*, and *Prevotellaceae* were positively correlated with HBsAg and HBeAg levels. On the contrary, *Akkermansia*, which is considered a gut barrier protector, was reduced in HBV mice and was negatively correlated with HBV DNA in both serum and the liver [167].

Extensive changes in the gut microbiota composition have been reported in patients with chronic HBV infection [168,169]. Decreased genera of bacteria that metabolize bile acids have been described in association with changes in serum and fecal bile acids in chronic hepatitis B (CHB) patients with moderate/advanced fibrosis. *Bacteroides* and *Ruminococcus* were significantly lower in CHB patients compared to healthy controls. It was

proposed that CHB fibrosis was in fact a modifier of the intestinal microbiota. Fibrosis limited the conversion of primary to secondary bile acids, activating the FXR and subsequently the FGF19 [170,171].

Microbiota changes already occur in early stage CHB patients. Operational taxonomic units (OTUs) belonging to *Actinomyces*, *Clostridium*, *Lachnospiraceae*, and *Megamonas* increased, while several OTUs decreased, including those belonging to *Alistipes*, *Asaccharobacter*, *Bacteroides*, and *Butyricimonas* [168]. The gut microbiota is also variable according to viral load. HBV patients with a low viral load have high diversity and taxa associated with fatty acid and lipid metabolism predominate [172]. LPS produced by Gram-negative intestinal bacteria was related to liver inflammation and cirrhosis. LPS levels were an independent predictor towards end-stage liver disease in patients with HBV infection [173]. Controversial results on the composition of microbiota have been reported. There was no difference in the intestinal microbiome between chronic HBV patients with normal ALT and normal volunteers. *Megasphaera* showed positive correlations, and *Acidaminococcus* exhibited a negative correlation with high ALT levels [174]. However, in another report, abundance of *Lactobacillus*, *Clostridium*, and *Bifidobacterium* were reduced in CHB patients with normal ALT compared to healthy controls [171]. In acute on chronic liver failure associated with HBV infection, the microbiota was enriched with *Moraxellaceae*, *Sulfurovum*, *Comamonas*, and *Burkholderiaceae*, but *Actinobacteria*, *Deinococcus-Thermus*, *Alphaproteobacteria*, *Xanthomonadaceae*, and *Enterobacteriaceae* were significantly reduced. Moreover, an increase of *Prevotellaceae* was a predictor of mortality [175].

In recent extensive studies, patients with all stages of HBV-related liver disease were examined and compared to healthy people. *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, *Cyanobacteria*, and *Fusobacteria* accounted for almost 100% of the total sequences. Decreased *Firmicutes* and increased *Bacteroidetes* were found in all disease groups (Chronic Hepatitis, cirrhosis, Hepatocellular carcinoma) compared to healthy controls. *Bifidobacterium* and butyrate-producing bacteria families such as *Clostridia* and *Ruminococcus* were also decreased in all disease groups [176], but no difference was observed among patients with resolved HBV infection [176,177]. These findings may have pathogenetic implications as *Bacteroidetes* are Gram-negative bacteria which produce LPS, while *Firmicutes* are Gram-positive bacteria without LPS synthesis. Therefore, the higher *Bacteroidetes/Firmicutes* ratio means increased burden of LPS to the liver cells and increased liver damage [178]. On the other hand, the *Enterobacteriaceae* family bacteria comprising many pathogenic bacteria such as *Klebsiella*, *Escherichia coli*, *Proteus*, and *Enterobacter* were increased in all HBV groups [176,179]. The *Enterobacteriaceae* family were also increased in liver cirrhosis and were positively correlated to Child-Pugh (CP) score [180,181]. In detail, a negative correlation was found between the CP score and *Bacteroidetes*, while a positive correlation was demonstrated between CP score and *Enterobacteriaceae* or *Veillonella* [182]. Apart from increased LPS secretion, the *Enterobacteriaceae* produce endogenous ethanol that may be detrimental to the liver [79]. In addition, high *Enterobacteriaceae* release endotoxin that may cause inhibition of enterocyte protein synthesis leading to increased intestinal barrier permeability with further bacterial translocation to the liver [183]. In fact, two studies reported on barrier permeability in CHB patients. In the first, serum zonulin and copeptin were reduced in CHB patients and were negatively correlated with serum HBV DNA [184]. This was in disagreement with another study where serum zonulin was higher in HBV-related HCC, but no difference was observed in patients with CHB, cirrhosis or healthy controls [185].

A repeatedly confirmed finding of gut dysbiosis during progression of chronic HBV is the decrease of SCFAs-producing bacteria, such as *Lachnospiraceae* and *Ruminococcaceae* and their replacement by LPS-producing bacteria such as *Enterobacteriaceae*, *Haemophilus*, and *Enterococcus* [165,186]. The microbiota of HBV carriers contains more SCFA producers and less pro-inflammatory bacteria than patients with CHB, cirrhosis, and acute-on-chronic liver failure or hepatocellular carcinoma [187,188]. Another consistent finding of dysbiosis in HBV patients is that *Bifidobacteria* decrease with the increase of *Enterobacteriaceae* as the

disease progresses. The ratio of *Bifidobacteria/Enterobacteriaceae* is reduced as disease severity progresses from CHB to cirrhosis and HCC [168,176,183,189].

Microbiota changes are difficult to be studied in human acute HBV. Results from animal studies have shown that the ratio of *Firmicutes/Bacteroides* increased early in the disease at day 14, and decreased in late disease at day 49 [166].

The above controversial reports indicate that interpretation and comparisons of results should be done with great caution as many studies are performed in populations with particular diet habits which influence the composition of the intestinal microbiome. Moreover, most studies are cross-sectional with samples representing an individual time point, and only a few were performed at different periods of HBV infection [165,187,190].

Detailed descriptions of the microbiome in the different stages of HBV infection have been recently published [191–194].

### 3.2. Microbiota and Immune Responses in HBV

Microbiota affects the immune response in HBV. Apart from the effects that LPS has on the immunological response through the activation of TLR4, an additional pathway is implicated in the immune response of patients with HBV. The unmethylated CpG DNA-TLR9 pathway can activate TLR9 that produces protective cytokines, such as Interferons. Unmethylated CpG DNAs is mainly produced by *Lactobacilli*, *Bifidobacteria*, *Proteobacteria*, and *Bacteroidetes* [195]. As mentioned above, *Lactobacillus* and *Bifidobacteria* are reduced in the gut microbiota of chronic HBV patients. Therefore, beneficial cytokines are reduced and the immune effects are defective in HBV [196,197].

Gut microbiota is implicated in the clearance of the HBV infection. When the gut microbiota is deregulated by antibiotics, the intestinal barrier function is probably impaired and the ability of immunity to clear HBV may be compromised [198]. Thus, adult mice with an intact intestinal microbiota clear HBV after 6 weeks of infection, while infection is not cleared in young mice or after antibiotic use [199,200]. Young mice with a TLR4 mutation achieved prompt HBV clearance. It therefore seems that a TLR4-dependent pathway of tolerance is operative in young animals and prevents HBV clearance. Development of intestinal microbiota stimulated the immune mechanisms and HBV clearance was feasible [201]. Additionally, impairment of intestinal microbiota was shown to affect the systemic adaptive immunity leading to delayed HBV antigen clearance. Gene analysis of Peyer's patches (PPs) demonstrated that adaptive immunity was downregulated in intestinal microbiota-deficient mice, while the depletion of PPs led to higher HBsAg levels in serum [202]. Dysbiosis in mice and the resulting endotoxemia induced IL-10 production by the Kupffer cells and increased Kupffer cell-mediated T cell suppression. The immediate result was the protracted persistence of HBV infection [203]. However, in a mouse model of CHB, intestinal bacteria reduction by antibiotics had no effect on HBV replication in immune tolerant mice [204].

The immune response in HBV infection is also regulated by metabolic products produced by intestinal microbes, such as tryptophan, which interferes with the immune response of HBV through its metabolic product kynurenine [205]. Indoleamine-2,3-dioxygenase (IDO) is an enzyme induced by interferon that catalyzes tryptophan into kynurenine [206] acting as a suppressor of intracellular pathogens and as an immune regulator [207]. Inducible IDO was shown to suppress HBV replication in HepG2 cells with the HBV genome [208]. The effect of IDO in HBV clearance was investigated in HBV infected patients. In acute hepatitis patients who finally cleared the virus, IDO activity was high at the peak of ALT. In patients with hepatic flare, on the other hand, IDO activity remained low irrespective of ALT levels indicating that IDO is an anti-HBV factor only during the early phase of HBV infection [209].

Integrated studies of microbiome and metabolome showed an extensive shift of intestinal microbiota and metabolites in chronic HBV patients attributed to either disease evolution and/or antiviral treatment. Peripheral mononuclear cells incubated with bacterial extracts (BE) from non-cirrhotic patients promoted the expansion of Th17 lymphocytes,

while BE from cirrhotics reduced Th1 cell count [210]. This is a particularly important findings that may explain some of the findings during liver fibrogenesis. Th17 immunity is an important factor in all stages of fibrogenesis in chronic HBV patients [211] including hepatic stellate cell activation [212,213], increased TGF- $\beta$  production [214], the secretion of matrix metalloproteases (MMPs), and collagen synthesis [212,214].

### 3.3. Microbiota and HBV Treatment

Based on the above findings, it was only logical to suggest that manipulation of the microbiome might be beneficial for the evolution of HBV. Fecal microbiota transplantation (FMT) was tested, but the data are still restricted [215,216]. In an interesting experiment, the gut microbiome in BALB/c mice was abolished by antibiotics and replaced with FMT from naïve mice to investigate the effect of FMT on the immune response to HBV infection. HBV clearance differed considerably depending on the origin of FMT. The fecal microbiota from C57BL/6 but not from BALB/c mice induced tolerance and prolonged HBV infection [217].

Gut microbiota changes, induced via FMT, resulted in promising results in HBeAg-positive patients. A study on HBeAg-positive CHB patients under treatment with oral antivirals showed that FMT induces HBeAg clearance in some cases who had failed to clear HBeAg despite long-term antiviral treatment. The problem with this study is that only five patients were studied in the FMT group [218]. In a similarly designed recent larger study of 14 patients in the FMT arm, 16.7% of patients cleared and none in the antiviral only arm. It should be noted, however, that all patients retained the HBsAg in either arm. However, after six months, serum HBV DNA was reduced in the FMT arm but not in the controls [219].

An informative review on all aspects of FMT has been recently published [215].

The effects of oral antiviral treatment on gut microbiota have also been examined in HBV. In a persistent HBV mouse model, *Akkermansia* was significantly reduced in HBV-infected mice, while Entecavir therapy restored levels back to those of the normal controls. *Akkermansia* levels showed a negative correlation with HBV DNA levels in serum and liver [167]. On the contrary, *Akkermansia* was increased in patients with CHB and liver cirrhosis [176]. Therefore, additional studies are required on the actual role of *Akkermansia* in HBV. In the treatment of naïve patients, *E. hallii* group and *Blautia* were greatly reduced and were restored to normal levels after 5 years of entecavir treatment. *Turicibacter* with 4-hydroxyretinoic acid were negatively associated with AST [210,220].

The manipulation of intestinal microbiota with probiotics (*Clostridium* and *Bifidobacterium*) was tested in the treatment of minimal hepatic encephalopathy (MHE) in patients with HBV cirrhosis. Probiotics improved serum ALT and AST and albumin levels. Absolute fecal bacterial load of genera *Fecal Clostridia* and *Bifidobacteria* were increased, and *Enterobacteriaceae* were decreased. More importantly probiotics improved psychometric tests and cognition. Ammonia levels were reduced possibly due to the observed improvement of the intestinal microflora [221]. A recent study administered a mixture of lactulose, *Clostridium butyricum*, and *Bifidobacterium longum infantis* in a population of patients with HBV-related cirrhosis. The clinical response was insignificant, but intestinal dysbiosis and the metabolome of the patients improved compared to patients treated with placebo [222]. Obviously, more extensive studies are required, particularly when the above expressed reservations are considered.

## 4. HCV Infection and Intestinal Microbiota

Globally, approximately 58.5 million people are infected with HCV worldwide, while 1.75 million new cases are identified each year. Hepatocellular carcinoma (HCV-related) causes approximately 150,000 deaths and more than 350,000 deaths are HCV-related other complications. These figures are probably an underestimation of the real problem [223].

Gut microbiota has been connected to the various stages of HCV infection. A common finding of all studies performed so far is the lower bacterial diversity in HCV patients compared to healthy controls [180,224–226]. Diversity abnormalities are proportional to

the stage of the disease [225]. Two hypotheses have been proposed that can explain how HCV infection can interfere with the gut–liver axis and the progression to fibrosis and cirrhosis. The first is that the gut microbiota is indirectly affected as a result of the liver damage. This is not compatible with changes in microbiota observed in early disease. The second hypothesis proposes a direct effect of HCV infection on B-lymphocytes and the consequent reduction of IgA production [224,227]. Reduced IgA secretion favors the abundance of *Prevotella*. *Prevotella* contains enzymes that may degrade mucin and increases the intestinal permeability leading to higher bacterial translocation [8]. A further indication of an impaired intestinal barrier in HCV-infected patients is also the finding of increased serum LPS levels [225,228].

Impairment of BAs metabolism is an additional explanation for the reduced microbial diversity in HCV. BAs profiles are different in chronic HCV compared with normal people. Fecal deoxycholic acid (DCA) was decreased and lithocholic or ursodeoxycholic acid predominated. The decrease in fecal DCA reduction was associated with *Clostridiales* reduction, while impaired synthesis of cholic acid (CA) was associated with a reduction in the transcription of CYP8B1, a key enzyme in CA synthesis [229]. This BAs disturbance results from overgrowth of pro-inflammatory bacteria, such as *Porphyromonadaceae*, *Enterobacteriaceae*, and reduction of *Firmicutes* the main producers of secondary bile acids [180,230–232].

The lower bacterial diversity is also associated with a reduction of the SCFAs producing *Clostridiales*, *Lachnospiraceae*, *Ruminococcaceae*, and an increase in *Streptococcus* and *Lactobacillus*, *Prevotella* and *Faecalibacterium* [227,230]. SCFAs are critical for the differentiation of bowel regulatory T (Treg) cells that are the main suppressors of inflammation [233,234] as mentioned before. Apart from *Clostridiales*, the phylum of *Firmicutes* is also decreased in patients with chronic CHC. By contrast, the phylum of *Bacteroidetes*, the family of *Enterobacteriaceae*, *Viridans streptococci*, and the genera *Bacteroides*, *Blautia*, and *Collinsella*, are increased [216,235]. A recent study also demonstrated a decreased diversity and found that *Lactic acid bacteria*, and *Lactobacillus acidophilus* were higher in early stage of fibrosis compared to patients with advanced fibrosis [236].

Low diversity is already evident even in patients with normal transaminases and minimal disease with a transient increase in *Bacteroides* and *Enterobacteriaceae*. Metagenomics have shown an increase in the urease gene encoded by *viridans streptococci* that may account for the hyperammonemia present in the later stages of the disease [232]. Similarly, bacterial translocation due to intestinal barrier dysfunction was reported in the absence of fibrosis, indicating that impairment of the gut barrier occurs even at the early stages of chronic HCV [173,237].

In contrast to all other reports, a recent study showed an increased microbiota diversity in patients with HCV infection compared to healthy individuals. A higher abundance of *Prevotella*, *Collinsella*, *Faecalibacterium*, *Megasphaera*, *Mitsuokella multacida*, and *Ruminococcaceae*, and a lower abundance of *Bacteroides*, *Alistipes*, *Streptococcus*, and *Enterobacteriaceae* was observed. Possible explanations for the discrepancy may be the stages of disease analyzed, the effect of HCV genotypes, and, most importantly, the demographic characteristics of the study groups [238].

An important finding was recently reported. The use of Proton pump inhibitors (PPIs) was related to significant alterations of the microbiota in patients with chronic HCV infection which were more pronounced in patients with liver cirrhosis. *Streptococcus* species, *Enterobacter* species, and *Haemophilus* species were significantly increased in patients with PPI use irrespective of the stage of liver disease [239].

Detailed descriptions of microbiota alterations in the different stages of progressive severity have been recently published [240,241].

#### *Effect of HCV Treatment on Intestinal Microbiota*

The initial treatment of HCV infection with interferon showed that the microbes before and after treatment were not different [242].

The use of effective direct acting antivirals (DAAs) in the HCV elimination prompted a series of studies of the potential effects of treatment on intestinal bacteria. The use of DAAs in patients with chronic HCV infection could only rectify the intestinal bacterial abnormalities only in with initial degrees of fibrosis [243]. A later study verified these results. Bacterial diversity was restored in patients without cirrhosis after sustained viral response (SVR) within 24 weeks after the end of treatment. No diversity improvement was found in SVR patients with cirrhosis. The abundances of *Collinsella* and *Bifidobacter* genera were increased between baseline and SVR only in non-cirrhotic patients [244]. However, in patients with genotypes 1,2,3 4 treated with glecaprevir/pibrentasvir, no significant differences in microbiota diversity, or microbial pattern were found before and after treatment at week 12 [245]. The same negative results were also very recently reported [246]. Two further reports also produced negative results. No significant alterations in the overall composition of gut microbiome or alpha diversity were observed after viral eradication. Some differences in abundance of certain bacteria, such as *Coriobacteriaceae*, *Peptostreptococcaceae*, *Staphylococcaceae*, and *Morganellaceae*, were identified but the overall compositions was not different after HCV eradication [247]. The diversity of the gut microbiota did not significantly alter before and after DAAs, even though the relative abundances of *Faecalibacterium* and *Bacillus* increased after eradication [248]. The reason for this discrepancy is not clear but the question is open to more detailed and larger studies.

The impact of DAAs on intestinal microbiota when cirrhosis is present also remains controversial as both favorable and negative studies have appeared and will be presented in the relevant section below [230,242].

Sustained viral response (SVR) seems to be a decisive factor, as alleviation of intestinal dysbiosis and microbial translocation were observed in responders but not in non-responders. Viral elimination increased the abundance of SCFAs-producing bacteria such as *Blautia* and *Bifidobacterium* [249]. However, successful response to DAAs eradication did not affect the intestinal barrier function. It is therefore likely that bacterial translocation is connected to abnormal composition of gut microbiota rather than to gut barrier dysfunction after DAAs therapy [230,249]. These reports are not consistent with findings demonstrating that microbial translocation markers, such as the lipopolysaccharide binding protein (LBP), were reduced after HCV elimination [250].

An interesting approach for restoration of gut dysbiosis is the use of Bacteriophages. In reality, phages are viruses that attack and eliminate bacteria [251]. The gut dysbiosis observed in HCV could potentially be corrected by using bacteriophages that target the chronic HCV associated bacteria [252], but this remains to be tested.

The current evidence on the effects of the gut microbiota in the evolution of HCV infection and the impact of DAAs elimination has been recently reviewed [31].

## 5. Other Hepatitis Viruses (A, D, and E)

Very limited information is available for these viruses, regarding mostly patients with acute hepatitis E (HEV) infection. The gut microbiota of these patients was enriched in *Proteobacteria*, and *Enterobacteriaceae* compared to normal controls. The presence of Gamma proteobacteria was positively related to ALT and total bilirubin levels and may be used as a predictor of the acute infection [253]. Significant changes were observed between acute uncomplicated HEV and HEV-associated acute liver failure (HEV-ALF). The HEV-ALF subgroup of patients had higher levels of *Gamma proteobacteria*, *Proteobacteria*, *Xanthomonadaceae*, and *Stenotrophomonas*, and decreased abundance of *Firmicutes*, *Streptococcus*, and *Lactobacillus*, when compared with the acute HEV group. The relative abundances of *Lactobacillaceae* and *Gammaproteobacteria* were positively correlated with Th lymphocytes, and degree of hepatic encephalopathy. Survival was associated with higher levels of *Lactobacillus mucosae* compared to deceased patients [254]. The administration of the probiotic bacterium *Enterococcus faecium* in pigs led to the reduction of enteric HEV viruses and accelerated viral clearance. However, no human trials have been performed [255].

The sporadic nature of acute Hepatitis A (HAV) prevented an extensive investigation of the intestinal microbiota. A Japanese study of an HAV outbreak among HIV positive patients showed significant microbe abnormalities and persistence of dysbiosis persisted for a long time after recovery [256].

No data about gut microbiota changes during hepatitis D virus (HDV) infection exist as of yet. This is almost impossible to be clarified since HDV infection always co-exists with HBV, meaning separate data are difficult to obtain [257].

## 6. Cirrhosis and Intestinal Microbiota

Chronic liver disease is associated with several abnormalities of the intestinal microbiome leading to reduced commensal diversity, expansion of pathogenic species and disruption of the intestinal defensive barriers [40]. Interestingly, microbial abnormalities in cirrhosis are independent of etiology [169,258,259]. Therefore, they are also applicable in viral cirrhosis as well.

Microbiome alterations were reported in alcohol-associated and hepatitis-associated cirrhosis [180]. Increased levels of *Veillonella*, *Megasphaera*, *Dialister*, *Atopobium*, and *Prevotella* genera were described in the duodenum of patients with cirrhosis. Interestingly, *Neisseria* and *Gemella* genera could differentiate between HBV and PBC cirrhosis [260]. The role of intestinal microbiota in non-alcoholic liver disease is possibly the most extensively investigated, but analysis is beyond the scope of the present review [261,262].

Reduced diversity, increased abundance of pathogenic species, such as *Staphylococcaceae* and *Enterobacteriaceae*, and decreased colonization by beneficial commensals such as *Lachnospiraceae* and *Ruminococcaceae* are all characteristics of cirrhosis. *Enterobacteriaceae* increase with progression of liver disease and decompensation [169,180,263].

Gut barrier disruption is well recognized in cirrhosis. It is due to reduced expression of the tight-junction proteins occludin and claudin [264]. In addition, the impairment of antimicrobial host defense, as demonstrated in experimental cirrhosis, allows for bacterial invasion of the inner mucous layer of the gut and increased bacterial translocation [265].

BAs are important regulators of the intestinal microbiome. Abnormalities in either the quantity or the composition of BAs in the intestinal lumen as observed in cirrhosis, will lead to a reduction of beneficial bacteria and an increase in pathogenic bacteria [153,266,267]. De novo suppression of BAs may be obtained by activation of the intestinal FXR-FGF19 pathway. As a consequence, the levels of *Firmicutes* and *Actinomycetes* with BSH activity will increase in association with up-regulated excretion of BAs from feces to protect from liver injury and fibrosis that otherwise would result from the toxicity of hepatic bile acids [268,269].

### 6.1. Involvement of Microbiota in the Pathogenesis of Cirrhosis

Portal hypertension, inflammation, and oxidative stress damage the gut barrier and participate in the complications of cirrhosis. The degree of the barrier damage and bacterial translocation parallels the severity of cirrhosis and the appearance of ascites [34,270]. A damaged barrier in cirrhosis is associated with restricted secretion of antibacterial peptides such as  $\alpha$ -Defensins by Paneth cells [271]. LPS overproduction by gut microbes activate Paneth cells to secrete angiogenic molecules that promote mesenteric angiogenesis and the development of portal hypertension [272]. LPS overproduction may also participate in the progression of liver fibrosis through interaction with the TLR4. Bacterial translocation promotes liver fibrosis and inflammation via activation of hepatic stellate cells and Kupffer cells [37,102]. LPS also activates the pattern-recognition receptor (PRR) mostly on macrophages, leading to the activation of quiescent HSC into myofibroblasts [273–276] and progression of fibrosis.

An additional pathway through which microbiota are engaged in the pathogenesis of cirrhosis is the activation of inflammasomes, the protein complexes found in most cells including Kupffer cells, hepatocytes, and HSCs [277,278]. They release pro-inflammatory cytokines such as IL-1 $\beta$  and IL-18 and promote inflammation and fibrosis in the liver [279,280].

TLRs and inflammasomes have different routes of activation [277], but their role is complementary in the communication between the gut microbiota and the systemic immune response [86]. Interestingly, TLRs may counteract the inflammatory activity of inflammasomes. Thus, chronic stimulation of the TLRs by LPS induces IL-10 production restricting inflammasome activation [281]. Moreover, the activation of TLR2 or TLR4 can upregulate the autophagy of hepatocytes that leads to the degradation of inflammasomes attenuating inflammation [282]. It should be noted that the interplay between intestinal microbiota portal hypertension and fibrosis resembles a mutual relationship, similar to that between the chicken and the egg, as they affect each other [283].

### 6.2. Microbiota and HE

The gut microbiota is a critical mediator in the interrelation between the liver and the brain. Gut dysbiosis influences the cognitive behavior of cirrhotic patients mediated by the gut–liver–brain axis [284–286]. The already described change of reduction of beneficial and overgrowth of pathogenic bacteria in cirrhosis is augmented as hepatic encephalopathy (HE) appears indicating a bidirectional relation between gut microbiota and the nervous systems of the body including the enteric nervous system, the autonomic nervous system, and the neuroendocrine and neuro-immunity systems of the central nervous system [287]. This microbial alteration further compromises the production of SCFAs in concert with increased barrier permeability and bacterial translocation [287,288]. Derangements of bile acids are also implicated in the pathogenesis of HE and the role of microbiota. Alterations in intestinal microbiota are associated with a reduced conversion of primary to secondary fecal BAs [259]. It has been shown that the serum conjugated BAs are increased in cirrhosis. During HE, there is a further increase in serum and brain BAs that can act as detergents increasing the permeability of blood–brain barrier and brain damage [289]. *Enterobacteriaceae* and fecal CDCA were correlated with the degree of HE, while *Ruminococcaceae* positively correlated with DCA. DCA is an effective bactericidal for gut microbes, and a lower DCA/CA ratio improves the cognitive function in HE [290].

Patients with acute HE were found to have decreased *Bacteroidetes* and an increase in the relative abundance of *Firmicutes*, *Proteobacteria*, *Actinobacteria*, and *Veillonella parvula* increased [291]. *Streptococcus salivarius* was also increased even in minimal HE with sleep disturbances and had a positive correlation with ammonia levels [292,293]. A positive correlation between cognitive impairment and the overgrowth of *Alcaligenaceae* and *Porphyromonadaceae* has been demonstrated. This is particularly important as *Alcaligenaceae* produce ammonia by decomposing urea [294,295]. Other Gram-negative bacteria containing urease such as *Streptococcus salivarius* and *Proteobacteria* also metabolize urea to ammonia and are implicated in the pathogenesis of HE [296].

The extensive variety of microbial species and their dependence on exogenous factors not related to cirrhosis itself may cause difficulties in comparisons among different studies. An example is the presence of minimal HE. Microbiota results may differ in various studies depending on the methods used for the diagnosis of minimal HE. Thus, the abundances of *Enterococcus* and *Streptococcus* were higher in minimal HE diagnosed by the psychometric encephalopathy score, while *Prevotella*, *Eggerthella*, and *Alistipes* species were higher when minimal HE was diagnosed by the inhibitory control test [297]. Only *Lactobacillaceae* estimations were not dependent on the method used for minimal HE diagnosis [298,299]. A way to partly overcome this problem in clinical studies is the use of gut dysbiosis indices. One such index is the Cirrhosis Dysbiosis Ratio, which is the ratio of the abundance of *Lachnospiraceae*, *Ruminococcaceae*, *Veillonellaceae*, and *Clostridiales Incertae sedis XIV* over this of *Bacteroidaceae* and *Enterobacteriaceae* [263]. Another index is the Gut Dysbiosis Index [168] where a high index corresponds with severe dysbiosis.

### 6.3. HBV Cirrhosis

The prevalence of HBV-related cirrhosis is lower in Europe and the Americas, compared to Africa and Asia while HCV-related cirrhosis has very heterogeneous prevalence. Globally, 42% of patient with cirrhosis had HBV infection and 21% HCV infection [300].

Specific intestinal microbiota alterations were described in HBV patients with cirrhosis. Prevalent phyla were *Firmicutes* (57%), *Bacteroidetes* (28.6%), with less abundant *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia*, adding up to almost 93% of the total sequences. *Bacteroidetes* were increased and *Firmicutes* were reduced HBV cirrhosis compared to the healthy individuals [194,301,302]. Patients with HBV cirrhosis had lower levels of beneficial bacterial taxa, such as *Dialister* and *Alistipes*, and higher levels of pathogenic species within *Actinobacteria* [165]. The lower *Firmicutes/Bacteroidetes* ratio may be pathogenetically associated with the progression of cirrhosis and inflammation. The *Bifidobacteria/Enterobacteriaceae* was decreased significantly in patients with decompensated HBV cirrhosis [183,303] while a reduced *Megamonas* genus level and increased *Veillonella* genus were risk factors for HBV-related liver cirrhosis [304]. In accordance with this scenario, *Akkermansia*, which is a protector of the intestinal barrier [305], was reduced in fecal samples of HBV cirrhosis with or without HCC [306,307].

Differences also exist between compensated and decompensated cirrhosis. Pathogenic bacteria, such as especially *Alcaligenaceae*, *Porphyrromonadaceae*, *Veillonellaceae*, and *Enterobacteriaceae*, significantly increased in the decompensation stage [194,215]. Interestingly, there are differences in the composition of gut microbiota when diabetes mellitus co-exists with HBV cirrhosis (LCDM). *Lactobacillus*, *Roseburia*, and *Veillonella* increased in the LCDM compared to HBV cirrhosis. Moreover, *Escherichia/Shigella*, *Veillonella*, and *Lactobacillus* showed a positive correlation with liver damage and fasting blood glucose [308]. HBV patients with decompensated cirrhosis have increased sIgAs content in blood and stool compared to asymptomatic HBV groups and controls. This is consistent with increased bacterial migration. *Enterobacteriaceae* were positively correlated with sIgAs [183]. Zonulin, a regulator of tight junctions and a marker of intestinal permeability [309] was significantly increased in HBV cirrhosis and HCC patients, correlating with the stages of cirrhosis [185]. However, in HBV-associated HCC patients, unexpected up-regulation of anti-inflammatory bacteria, such as *Prevotella* and down-regulation of pro-inflammatory bacteria, like *Escherichia*, were reported in comparison to non-hepatitis-related HCC [179].

### 6.4. HBV-Related HCC

It is clearly established that the gut microbiome may influence the induction and progression of HCC by interfering with immune and metabolic pathways related to HCC. Data, both experimental [310] and clinical, mostly exists for non-viral HCC [311–315]. Recent findings have demonstrated that this is also true for HBV related HCC. Overgrowth of pathogenic bacteria of Gram-negative species and a significant increase in the fecal count of *Escherichia coli* are characteristic in HBV-related HCC [316]. Butyrate-producing bacteria, such as *Ruminococcus*, *Oscillibacter*, *Faecalibacterium*, *Clostridium IV*, and *Coproccoccus*, were limited, while the LPS-producing bacteria *Klebsiella* and *Haemophilus* were augmented compared to cirrhosis patients [188,307].

Increased *Prevotella* abundance was also described in HBV-HCC compared to non-viral HCC [179]. Finally, changes in BA metabolism may contribute to the pathogenesis of HCC. Modifications of BAs metabolism by intestinal microbiota have already been described in HBV infection. Therefore, their implication in HBV-HCC induction is highly probable [317].

### 6.5. HCV Cirrhosis

As in HBV related cirrhosis, a reduced microbial diversity was reported in HCV cirrhotics compared to healthy individuals. Thus, higher levels of *Prevotella* and *Faecalibacterium* and lower levels of *Acinetobacter*, *Veillonella*, and *Phascolarctobacterium* were observed in the intestinal microbioma of Egyptian patients. Moreover, the ratio *Prevotella/Bifidobacterium* was proposed as a marker of fibrosis development [224]. Detailed

descriptions of the diversity of microbial species in HCV cirrhosis have been recently presented. Thus, higher levels were found for *Veillonella*, *Lactobacillus*, *Streptococcus*, *Alloprevotella*, *Bifidobacterium*, *Escherichia/Shigella*, *Haemophilus*, *Micrococcus*, and *Weissella* species. On the other hands *Bilophila*, *Clostridium*, *Mitsuokella*, and *Vampirovibrio* species were significantly decreased. Interestingly, the beneficial *Akkermansia* series were also significantly increased [225,240,318].

Table 1 graphically depicts the main microbiome changes in chronic viral liver disease. It should be stressed however, that there are many discrepancies as the results are dependent on a variety of external factors.

**Table 1.** Main Microbiome alterations in chronic viral liver disease. See text for details. Bidirectional light arrows indicate controversial results. Upward arrows indicate increase. Downward arrows indicate decrease.

Healthy Individuals Phyla	Genera	Chronic HBV	Chronic HCV	Cirrhosis	Hepatic Encephalopathy	HCC
Proteobacteria	Escherichia Klebsiella	↑		↑	↑	↑↓
						↑
Firmicutes	Clostridia Blautia Enterococcus Ruminococcus Lactobacilli Streptococci	↓	↓	↓	↑	↓
		↑	↑	↑	↑	↑
		↓	↑↓	↓	↑	↓
		↓	↑	↑	↑	↓
		↓	↑	↑	↑	↓
		↓	↑	↑	↑	↓
Actinobacteria	Bifidobacteria Collinsella	↓	↑	↓	↓	↓
Bacteroidetes	Bacteroides Prevotella	↓	↓		↓	
		↑	↑	↑	↑	↑
Verrucomicrob	Akkermansia	↑↓		↓↑		

The effect of treatment on gut microbiota has been examined in HCV-related cirrhosis. Treatment with pegylated interferon and ribavirin did not improve the composition of intestinal microbiota, even in those achieving SVR [242]. The effects of treatment with direct acting antivirals (DAAs) are controversial. DAAs administration modified the composition of the gut microbiota and reduced dysbiosis after achievement of SVR. The levels of pathogenic *Enterobacteriaceae*, *Enterococcus*, and *Staphylococcus* were decreased after treatment. However, intestinal barrier permeability was not affected [230]. A recent study reported that modifications of the gut microbiota after DAAs treatment was only observed in the absence of cirrhosis. No significant differences were observed in cirrhotic patients [244]. Recently, a small longitudinal study of patients with HCV-related cirrhosis and clinically significant portal hypertension was reported. Treatment with DAAs modi-

fied significantly the gut microbiome only in those with a significant reduction of portal pressure [319].

Fecal microbiota transplant may also improve gut dysbiosis and the intestinal microbiota in minimal HE as shown in two small studies that included a number of HCV patients [320,321]. Contrary to expectations, lactulose administration in cirrhotic patients did not affect intestinal microbiota. The study population included cirrhotic patients of mixed etiology, half of them patients with HBV and HCV cirrhosis. Phyla such as *Tenericutes*, *Cyanobacteria*, *Spirochaetes*, *Elusimicrobia*, and *Lentisphaerae* were lower in cirrhosis and did not change after lactulose [322]. This was not the case in a study of minimal HE patients, with half of them being HCV-related [323]. This is also in disagreement with a more recent study of patients with viral cirrhosis, where administration of lactulose improved the cognitive abilities of cirrhotic patients and alleviated microbiota dysbiosis in minimal HE. In addition, lactulose responders had significantly different *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Proteobacteria*, compared to non-responders [324].

Table 2 summarizes the results of therapeutic modulations in the microbiota of chronic viral liver disease.

**Table 2.** Therapeutic Manipulation of the microbioma in chronic viral liver disease. Upward arrows indicate increase. Downward arrows indicate decrease.

Treatment	HBV Cirrhosis	HCV Cirrhosis	Hepatic Encephalopathy	Reference
Lactulose	Improvement but all phyla increased in non-responders	No change	Bifidibacteria ↑ Bact. Translocation ↓	[322–324]
Rifaximin	Improvement Eurobacteriaceae ↑ Veillonellaceae ↓			[325]
Probiotics	Diversity, dysbiosis ↓ No change in cognition Enterobacteriaceae ↓ Clostridiales ↑ Clostridia ↑ Bifidobacteria ↑ Firmicutes ↓ Streptococcae ↓ Clostridia ↓ Lactobacilli ↑			[221,326–328]
Synbiotics	Improvement Lactobacilli ↑			[329]
Fecal Transplant	Dysbiosis ↓ Diversity ↑ Ruminobacteria ↑ Bifidobacteria ↑ Streptococcus ↓ Veillonella ↓ HBeAg clearance ↑		Improved cognition Bifidobacteria ↑	[218,219,321,328]
Entecavir	E. Hallii ↑ Blautia ↑ Ruminococcus ↑ Akkermansia ↑			[167,210]

Table 2. Cont.

Treatment	HBV Cirrhosis	HCV Cirrhosis	Hepatic Encephalopathy	Reference
DAAAs		Enterobacteriaceae ↓ Staphylococcus ↓ Dysbiosis ↓ Diversity increased only after reduction of Portal Hypertension No change Dysbiosis ↓ Collinsella Bifidobacterium Only in non-cirrhotics No difference before and after SVR No change in diversity Faecalibacterium ↑ Bacillus ↑		[230,242,244,245,247,248,319]

## 7. Conclusions

Gut microbiota is in constant communication with the liver microenvironment, affecting both hepatocytes and sinusoidal cells through the gut–liver axis. As in other chronic liver diseases, all the components of this communication are seriously affected in HBV and HCV infections. Intestinal barrier abnormalities lead to increased translocation of bacteria or their components that activate both innate and adaptive immunity in the intestinal lamina propria with subsequent activation of TLRs and various signaling pathways. A constant finding is the reduction of microbial diversity. Beneficial bacteria are reduced, and potential pathogens are increased. Thus, decreased *Firmicutes* and increased *Bacteroidetes* are found in all viral disease groups compared to healthy controls. Moreover, *Bifidobacterium* and SCFAs-producing bacteria families, such as Clostridia and *Ruminococcus*, also decreased in all disease groups. The changes are usually more pronounced as viral hepatitis progresses to cirrhosis and hepatocellular carcinoma. Based on these microbial alterations, specific treatments are tested. Fecal microbiota transplantation is tried with satisfactory results, mostly as an adjunct therapy in antiviral treatment of HBV and HCV or in patients with cirrhosis and hepatic encephalopathy. The same groups of patients are also treated with various combinations of probiotics with promising results. Attempts to strengthen the intestinal barrier by drugs or modulation of TLRs responses have not yet been tried in viral liver disease.

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