**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 63355

**Manuscript Type:** REVIEW

**Microbiota and viral hepatitis: State of the art of a complex matter**

Russo E *et al*. Gut microbiota and hepatitis

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**Author contributions:** Russo E and Milosevic I equally contributed; Russo E, Milosevic I and Amedei A conceptualized the review; Milosevic I, Barak A, Vujovic A and Russo E wrote the paper; Milosevic I, Barak A, Vujovic A, Stevanovic O, Russo E performed the collected the data; Milosevic A, Barak A and Vujovic A, prepared the figures; Gitto S and Amedei A corrected the final version; Barak A, Russo E, Amedei A Funding Acquisition; All authors did critical revision of the manuscript

**Supported by** the Italian Ministry of University and Research (MIUR), the Foundation ‘Ente Cassa di Risparmio di Firenze’, No. FCR 2017.

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**Received:** February 2, 2021

**Revised:** March 26, 2021

**Accepted:** July 21, 2021

**Published online:**

**Abstract**

Changes of gut microbiota influence both the gut and liver, which are strictly connected by the so-called “gut–liver axis”. The gut microbiota acts as a major determinant of this relationship for the onset and clinical course of liver diseases. According to the results of several studies, gut dysbiosis is linked to viral hepatitis, mainly hepatitis C virus and hepatitis B virus infection. Gut bacteria-derived metabolites and cellular components are key molecules that affect the liver function and modulate the pathology of viral hepatitis. Recent studies showed that the gut microbiota produces different molecules, such as peptidoglycans, lipopolysaccharides, DNA, lipoteichoic acid, indole-derivatives, bile acids, and trimethylamine, which are translocated to the liver and interact with liver immune cells causing pathological effects. Therefore, the existence of crosstalk between the gut microbiota and liver and its implications on host health and pathologic status are essential factors impacting the etiology and therapeutic approach. Concrete mechanisms behind the pathogenic role of gut-derived components on the pathogenesis of viral hepatitis still remain unclear and not understandable. In this review, we discussed the current findings of the research on the bidirectional relationship of the components of gut microbiota and the progression of liver diseases and viral hepatitis and *vice versa*. Moreover, this paper highlights the current therapeutic and preventive strategies, such as fecal transplantation, used to restore the gut microbiota composition and so improve host health.

**Key Words:** Gut microbiota; Hepatitis B; Hepatitis C virus; Liver diseases, Fecal transplantation

Russo E, Milosevic I, Vujovic A, Barac A, Stevanovic O, Gitto S, Amedei A. Microbiota and viral hepatitis: State of the art of a complex matter. *World J Gastroenterol* 2021; In press

**Core Tip:** Changes within the gut microbiota have an impact on the mutual crosstalk between intestinal microbiota and liver. Gut dysbiosis is linked to viral hepatitis, mainly hepatitis C virus and hepatitis B virus infection. However, concrete mechanisms behind the pathogenic role of gut-derived components on the pathogenesis of viral hepatitis still remain unclear. We discuss the recent studies to well-understand the role of gut microbiota.

**INTRODUCTION**

The gut contains a large, complex microbial community that has much more genetic material than the total human genome[1]. Gut microbiota (GM) acts as a major determinant of complex bidirectional communication between gut and brain to maintain the intestinal homeostasis and host health[2,3]. However, the bacteria of gastrointestinal tract produce several enzymes, metabolites, and cellular components that can contribute to many disorders such as liver disease[3], diabetes mellitus[4], inflammatory bowel disease[5], irritable bowel syndrome[6], obesity[7], colorectal cancer[8], and mental illness[9].

The term gut-liver axis refers to the anatomical and physiological connection between the gut and liver[3]. The gut-liver axis is based on the very close anatomical relationship of these organs and consequently, enzymes, metabolites, and immune signals are transferred to the liver through the portal vein circulation[10-12]. These gut-derived metabolic products modulate immune functions and moderate liver disease formation, pathogenesis and treatment responses, by acting as signaling molecules[10-13].

The GM definitely represents one of the main factors influencing the gut-liver axis and its role in the alteration of liver function has recently received considerable attention[3].

Gut dysbiosis may specifically lead to an inflammatory response by increased production of the pro-inflammatory cytokines, which are recognized by receptors in the portal circulation[10,12,14]. Production of these pro-inflammatory cytokines largely depends on the response of the innate immune system to the presence of microbial products[12]. It was documented that the GM profile in patients with chronic hepatitis differs considerably from that observed in healthy patients[15,16]. Moreover, the degree of liver insufficiency is closely related to the severity of gut dysbiosis[10]. Recent studies supported the fact that GM dysbiosis helps the advancement of hepatitis viral infection[17]. During chronic viral hepatitis, the intestinal microbiota has a great impact on viral host cell interaction as well as on viral replication[18]. *Escherichia coli (E. coli*), *Enterobacteriaceae*, *Enterococcus faecalis*, and *Faecalibacterium prausnitzii* represent the most harmful bacteria that can alter the good profile of GM in viral hepatitis and consequently lead to a decreased number of lactic acid species[19,20]. In addition, an increased number of *Candida sp*. in the stool is usually detected in patients with progression of hepatitis B virus (HBV), while *Neisseria,* *E. coli*, *Enterobacteriaceae*, *E. faecalis, F. prausnitzii*, and *Gemella* are the most common bacterial species present in GM of the patients with HBV and hepatitis C virus (HCV) infection and correlated with progression of liver disease[20-22].

This review paper provides an overview of the state of the art of this complex matter. We discussed the recent updates of the interactions of GM, liver diseases and viral hepatitis and potential therapeutic interventions that target the gut–liver axis.

***GM in pathologic liver***

As previously mentioned, the liver and intestine extensively interact *via* the biliary tract, the portal vein and the systemic mediators. The liver is a crucial immunological organ, mainly enriched with innate immune cells and persistently exposed to numerous circulating nutrients, microbial components and metabolites in close contact with the intestinal tract. Liver compounds, on the other hand, mainly affect the GM structure and integrity of the gut barrier, while intestinal conditions control the synthesis of bile acids, glucose and lipid metabolism in the liver. Currently, many lines of research have established a relationship between the GM and liver disease. Indeed, a concurrent surge in liver diseases and gastrointestinal and immune disorders confirms the crosstalk between the gut and the liver[23]. Among the liver illnesses, the pathogenesis and progress of non-alcoholic fatty liver disease (NAFLD) and the most severe form non-alcoholic steatohepatitis (NASH), alcohol-related liver disease (ALD), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), cirrhosis and hepatocellular carcinoma (HCC) have been associated with changes in the gut-liver axis[24]. In the light of these evidences, latest advancements in the understanding of the gut-liver axis support studies to enhance liver disease treatment in microbiome-based, diagnostic, prognostic, and therapeutic modalities.

**NAFLD**

A large number of preclinical and clinical studies from the last decade have investigated the role of the GM in NAFLD and NASH, showing different results. In general, NAFLD patients display a decreased GM diversity[25,26], with a decrease of Bacteroidetes and Firmicutes, along with an increase of *Lactobacillus*[27]. Moreover, steatosis was related with abundance of *Ruminococcus gnavus* and *Coprococcus* and lower bacterial diversity in NAFLD[28] while NAFLD severity was related to shifts in both GM composition and metabolic functions[29,30]. Recently, a correlation between specific immune cells and GM fecal signatures was observed in NAFLD. In detail, *Faecalibacterium prausnitzii* was negatively correlated with CD163+ and CD45+ cells while *Prevotella* was negatively correlated with CD20+ cells[31]. In addition, a GM signature was demonstrated also in fibrotic NASH[32] where advanced liver fibrosis was related to augmented *Proteobacteria* levels, whereas Firmicutes were significantly decreased[32]. Patients with NASH also showed decreased *Faecalibacterium* *prausnitzii*, *Ruminococcus*, and *Coprococcus* abundance in comparison with healthy controls[27], while paediatric patients exhibited an increased abundance of *E. coli*[25]. In NASH patients, bacterial overgrowth can inhibit intestinal tight junction function and encourage epithelial barrier dysfunction[33]. Whereas several reports have evaluated the GM, much less is reported about the virome, defined as the total collection of viruses in and on the human body. A more advanced NAFLD was associated to viral (and relative bacteriophages) diversity decreasement[34]. Additionally, a recent panel including microbiota features was able to detect NAFLD-cirrhosis[35], providing evidence for a fecal-microbiome derived profile to detect NAFLD. A choline based diet has been shown to be compatible with NAFLD by GM structure changes that benefit bacteria that break down choline[36]. A very recent animal model research, however, revealed sex variations in GM abundance changes, behaviors, and hepatic steatosis in response to dietary copper-fructose interaction in rats[37]. Finally, a particular symbiotic used for the therapy changed the fecal microbiota in a placebo-controlled trial, but failed to change hepatic steatosis in subjects with NAFLD[38].

**ALD**

Several researches were conducted in mouse and human models based on how alcohol can induce dysbiosis associated with microbiota, which in turn can lead to ALD pathogenesis and development[39]. Regarding the GM composition, ALD patients show lower levels of *Bifidobacterium*, *Enterobacterium* and *Lactobacillus* *spp*.[40-43], while cirrhotic patients with ALD showed an important reduction in Firmicutes and Bacteroidetes phyla[23,44]. In fecal samples, a reduction in the *Lactobacillus spp*., has been observed in alcoholic patients whereas cirrhotic patients showed lower amounts of *Bifidobacterium spp*.[45,46]. In addition, the GM of alcoholics with liver cirrhosis contained increased levels of *Enterobactericeae[*41]. In general, an increase in the amount of microorganisms was found in the small bowel of alcoholic patients[47-49], with higher levels of microbial metabolites in the blood compared to healthy controls[19,50]. During ALD progression, a shift in the GM profile from steatohepatitis to pre-cirrhosis to cirrhosis has been reported[51]. In addition, research on chronic alcoholics have demonstrated that bacterial overgrowth is central to disease progression[52]. These findings are also supported by mouse studies[53]. In addition, research on chronic alcoholics have demonstrated that bacterial overgrowth is central to disease progression[54]. Alcohol-associated dysbiosis can decrease biosynthesis of long chain fatty acids (LCFA) in mice and LCFA supplementation can restore eubiosis. In fact, a significant correlation between *Lactobacillus spp*. and bacterial LCFA has been observed in ALD patients[55]. Alcohol can also reduce the development of butyrate and the administration of butyrate modulates alcohol-induced liver damage in mice[56].

**PBC**

Patients with PBC show a significant general decrease of bacterial diversity[57]. Indeed, *Bacteroidetes spp.* were significantly decreased and *Haemophilus*, *Fusobacteria*, *Clostridium*, *Veillonella*, *Lactobacillus*, *Pseudomonas,* *Streptococcus*, *Klebsiella*, *Proteobacteria spp.* and *Enterobacteriaceae* were over-represented in PBC patients compared to healthy controls[57]. A cross-sectional research has shown that GM, metabolism and immune alterations are associated in PBC patients[58]. In detail, beneficial intestinal microbes, including *Lachnobacterium* spp., *Acidobacteria*, *Ruminococcus bromii* and *Bacteroides eggerthii*, were found depleted and higher levels of opportunistic pathogens, such as *Enterobacteriaceae*, y-*Proteobacteria*, *Neisseriaceae*, *etc*., were reported[58]. In the same study, PBC-related GM modulation was associated with increased markers of liver damage and serum inflammatory cytokinesis[58]. Moreover, a recent study[59] demonstrated that the concentration of particular secondary bile acids inversely correlates with upregulated microbes in PBC patients but positively correlates with upregulated bacteria in healthy controls[59]. Relationships between clinical profiles, reaction to treatment with ursodeoxycholic acid and GM composition in patients with PBC have recently been studied[60],suggesting the decrease in *Faecalibacterium* as an innovative prognostic element in PBC.

**PSC**

Several reports investigating the role of GM in PSC show an overall reduction in GM diversity[61]. Alterations in biliary and fecal microbiome in PSC patients are characterized by higher abundances of *Lactobacillus*, *Fusobacterium*, and *Enterococcus* and low diversity[62,63]. In addition, PSC patients showed an overrepresentation of *Enterococcus*, *Rothia*, *Clostridium*, *Streptococcus*, *Haemophilus*, *Veillonella*, *Fusobacterium* and *Lactobacillus* genera[64,65]. In particular, *Veillonella* abundance was clearly increased in PSC patients matched with healthy controls[63]. Furthermore, the GM profile of PSC intestinal biopsies was distinguished by *Barnesiellaceae* abundance and a decline in *Clostridiales*[66,67]. The pathogenesis of PSC was linked with GM dysbiosis by causing *bacterobilia*, which in turn stimulates a proinflammatory mechanism contributing to fibrosis and inflammation in the cholangiocytes[68,69].

***HBV infection***

Liver failure and disease progression in patients with chronic HBV infection is found to be connected to GM dysbiosis in a large proportion[18,70]. There are differences in the composition of the intestinal flora between the patients with HBV and HCV infection (Figures 1 and 2). Compared to healthy controls, patients with chronic HBV infection showed abundant *Anaerostipes* taxon[71,72]. Liu *et al*[70] aimed to find the differences in the GM composition of HBV and non-HBV non-HCV related HCC compared with healthy controls. HCC patients with HBV were found to harbor higher species richness, more potential anti-inflammatory bacteria (such as *Prevotella*, *Faecalibacterium*, *Pseudobutyrivibrio,* *Lachnoclostridium*, *Ruminoclostridium*), and fewer pro-inflammatory bacteria (such as *Escherichia-Shigella*, *Enterococcus*) while *Proteobacteria* abundance was decreased. The role of anti-inflammatory bacteria such as *Faecalibacterium* and *Prevotella* is in their anti-inflammatory and anti-carcinogenic potential[73], but HBV infection leads to its progressive decline compared to healthy subjects[70]. In addition, Ren *et al*[74] documented the butyrate-producing bacteria declined in early HCC HBV positive patients. This further indicated that HBV indeed plays a role in GM changes. In HBV infection, a beneficial bacterium, *Lachnospiraceae*, plays a role *via* reduction in lipopolysaccharide (LPS) section and bacterial translocation[74,75]. A study of Lu *et al*[16] suggests that cirrhotic patients with HBV infection exhibit a decrease in *F. prausnitzii*, *E. faecalis*, *Enterobacteriaceae*, *Bifidobacteria* and lactic acid bacteria, while *Enterococcus* and *Enterobacteriaceae* levels are significantly increased compared to healthy individuals.

On the contrary, HBV and HCV negative patients with HCC harbored fewer potential anti-inflammatory bacteria and more pro-inflammatory bacteria. Taken together, these data implicated that GM plays an important role in the progression of HBV or non-HBV non-HCV related HCC. These findings were different from previous reports about HBV induced liver diseases[16,70,76]. The discrepancy in these findings was probably due to the progression of liver diseases and the group of patients in evaluated studies. To analyze the GM role in HBV positive patients, it is appropriate to use a defined cohort of patients suffering from HBV infection[77], excluding patients with different etiologies of liver cirrhosis (including alcohol abuse) that itself may change the composition of the intestinal microbial community and the same might be true for other liver diseases[70,78]. Therefore, the discrepancy of fecal microbiota between the HBV positive and HBV negative patients in the study of Liu *et al*[70] perhaps ascribe to the HBV infection[70,77].

Not only gut dysbiosis, but also dysbiosis of the oral microbiota was observed in HBV patients, and yellow tongue coating is suggestive of a reduction in *Bacteroidetes* but an increase in *Proteobacteria*. Zhao *et al*[79] also suggested a positive correlation between the serum HBV-DNA and number of *Neisseriaceae* in oral microbiota.

Furthermore, the GM composition differed according to the level of alanine aminotransferase (ALT) in HBV patients[80,81]. *Desulfovibrio* had a positive correlation, while *Acidaminococcus* showed a negative correlation with a high ALT level[81]. Lu *et al*[16] found a significantly decreased ratio of *Bifidobacteriaceae/Enterobacteriaceae* (B/E) in cirrhotic HBV positive patients, while Yun *et al*[72] observed no difference in the B/E ratio in non-cirrhotic HBV patients with positive HBsAg and normal or high ALT. These findings lead to the conclusion that B/E ratio is disturbed only in GM of patients with cirrhosis. However, another study observed that the *Megasphaera* genus of the Firmicutesphylum was abundant in the HBsAg positive high ALT group compared to the normal ALT group. In HBsAg positive patients with normal ALT, butyrate-producing bacteria (*e.g.*, *Anaerostipes*) are more often present in GM compared to HBsAg- patients[72]. These bacteria produce short-chain fatty acid as a by-product of lactate fermentation and butyrate. In Figure 1 we have reported the main microbiota alteration in HBV.

Recently, Wang *et al*[82] defined the serum zonulin as an intestinal permeability marker and showed its association with AFP levels in HBV-associated liver cirrhosis and HCC, especially helpful in correlating it with advanced stages of the diseases[83]. It has been reported that the diagnostic model of one location may be not used in other locations, since especially the diagnostic efficiency declined when the geographic scale was increased[79]. The characteristic GM changes had the strongest relationship with the host location, thus, the diagnosis potential of microbial markers should be considered the geographic differences[79].

***HCV infection***

The liver-gut interaction controls the GM homeostasis during HCV infection, which might be an ideal model to study the interaction between the GM and liver[18,80]. The review of previous reports provides the rationale for the hypothesis that GM dysbiosis could also be employed as a biomarker and a therapeutic target to mitigate disease progression. Interestingly, HCV-RNA and HCVcoreAg were frequently found in the stool of patients with chronic HCV[84]. Therefore, direct interactions between virus particles and intestinal bacteria might facilitate or inhibit growth like in rotavirus infection[85]. Heidrich *et al*[86] found that progression of HCV infection is connected to a reduced alpha diversity revealing that the relative abundance of phylotypes are associated with the stage of the disease. Additionally, Sultan *et al*[2] characterized the GM from the cohort of adult patients with HCV before starting any treatment and confirmed the presence of GM dysbiosis. Microbial taxa in HCV positive patients identified during this study were characterized by increased microbiota diversity, the enrichment of *Enterobacteriacea*, *Prevotella*, *Coriobacteriaceae*, *Megasphaera*, *Succinivibrio*, and *Ruminococcaceae*, and the depletion of *Bacteroides* and *Streptococcus*. In addition, GM of HCV-infected subjects was characterized by the depletion of carbohydrates and lipid metabolism, specifically galactose, fructose, mannose, and sphingolipid metabolism. In the presence of HCV infection microbiota-associated histidine metabolism was decreased, while metabolism of cysteine and methionine and translation proteins were enriched compared to the healthy controls[2]. The findings of Sultan *et al*[2] contradict the previous literature that showed a decrease in GM diversity and changes within the abundance of some taxa like *Prevotella*, *Ruminococcaceae*, *Enterobacteriacea*, and *Faecalibacterium* in patients with chronic HCV infection[2,15,86-88]. This could be because of the many aspects like different stages of the disease, treatment or other medication-related factors, different genotypes, demographics, diet, alcohol consumption or smoking. Specifically, treatment regimens were not controlled in most of these reports, which may obscure a possible key microbe, a protective role, or a diagnostic-related signal. The impact of the specific treatment received significant attention in GM research in other health disorders as well[5,89,90].

It was documented that antiviral HCV treatment with ribavirin + pegylated interferon has no direct impact on gut dysbiosis, and in fact, it increases the bile acids, which is very important for GM metabolism[91]. Some pathogenic bacteria like *Enterobacteriaceae*, *Staphylococcus*, and *Enterococcus* decreased the steroid in HCV-infected cirrhotic patients, which normalized after direct-acting antivirals (DAAs). In addition, DAAs are helpful in improving GM, especially from the *Lachnospira* and *Dorea* genera, and in restoring TNF-α levels[92]. After DAAs’ treatment, however, expression of calprotectin, ZO1, and LPS was more intensive in HCV patients with cirrhosis[92]. Pérez-Matute *et al*[92] showed that the administration of DAAs in HCV patients is not able to improve GM bacterial richness. However, partial restoration in inflammation, alpha diversity and a few bacterial genera (except *Actinobacteria*) were observed after 3 mo in patients with a lower fibrosis degree, stressing the concept that gut dysbiosis and liver damage are gradual[92]. Liver fibrosis degree might be a key factor that contributes to a definite GM profile. A lower abundance of *Akkermansia municiphila* is additionally found in HCV infected patients with higher fibrosis degrees and it is proposed that these bacteria could have a major role in the evolution of HCV infection and liver damage. *Akkermansia municiphila* is proposed as a new candidate for developing novel supplements with beneficial effects for GM recovery[93] and to intensify the DAAs’ actions at this level. These results confirm those previously observed with former treatments in cirrhotic patients[94]. Thus, with severe liver damage, a greater impact on GM is observed, and, therefore, there are more difficulties to counteract such changes with antivirals. These data highlight the need to treat patients as soon as possible in order to reverse the negative actions caused by HCV infection on GM diversity and future clinical correlated consequences.

It was found that *Blautia*, *Coprococcus*, and *Dorea* genera are increased in HCV positive patients, what is opposite to the lower presence of these bacteria observed in the disease stage 4[95]. Such conflicting findings could be explained by the various fibrosis degrees of the study groups. Several studies have demonstrated an over-representation of *Veillonella* in cirrhotic patients (both, HBV and/or HCV infected) and its positive correlation with ALT or AST levels in serum[20,75,92]. In conclusion, the role of this genus in GM of healthy people is not completely revealed.

The increased presence of *Lactobacillus* in HCV-infected patients was found in very few studies, although the studies’ cohorts were not uniform (treatment-naïve and patients under treatment regimen)[86,92]. However, the impact on the progression of HCV infection of this genus and a few bacterial species belonging to that genus (such as *L. ruminis*) has to be specifically addressed, since some probiotics are supported bacterial strains belonging to this genus[96]. In Figure 2 we have reported the main microbiota alteration in HCV infection.

The GM varies in patients with different HCV genotypes[86]. Statistically significant differences in GM composition between patients with and without liver cirrhosis are only found in genotype non-1. In genotype 1 differences in the microbial composition are associated with the persistent HCV infection rather than with the fibrosis stage. Therefore, studies investigating patients with liver diseases compared to healthy controls might overlook the influence of the underlying disease on the intestinal microbial communities, and so other diseases and stages of diseases need to be investigated for the potential associations[15,75].

***Cirrhosis***

A recent study has shown that GM has lower abundance of *Bacteroidetes* and higher levels of *Prevotella*, *Enterococcus*, *Veillonella*, *Proteobacteria*, *Megasphaera*, *Burkholderia*, and *Fusobacteria* in patients with cirrhosis[20,43]*.* In the duodenal mucosal of cirrhotic patients, an overrepresentation of *Veillonella*, *Megasphaera*, *Dialister*, *Atopobium*, and *Prevotella* was reported, compared to controls. A reduction in diversity, a rise in immunostimulatory pathogens (*e.g.*, *Staphylococcaceae* and *Enterococcaceae*) and a decline in potentially beneficial *Firmicutes* (*e.g.*, *Ruminococcaceae* and *Lachnospiraceae*) have been identified with respect to the fecal microbiota in patients with cirrhosis[15]. Moreover, similar changes can be detected in the colon mucosa[97], serum[98], and saliva[99] of patients with cirrhosis. Interestingly, the improvement in the GM composition was correlated with the outcomes of patients with (*i.e.*, compensated *vs* uncompensated[100], inpatient *vs* outpatient, and noninfected and infected patients[19]), indicating microbiota alterations as potential new biomarker. Intriguingly, higher abundance of buccal-derived microflora was recorded in fecal specimens of cirrhosis patients, as well as dramatically altered salivary microbiome levels[15]. In a very recent and innovative study, an analogous microbiome profile was observed independently of the etiology of cirrhosis by using a machine-learning-based methodology and matching their outcomes with other cohorts containing different etiologies of liver cirrhosis. These outcomes suggest that the etiology of liver disease tends to be less relevant regarding the GM alterations[101]. Such an approach may allow the non-invasive diagnosis of cirrhosis of the liver[101].

***HCC***

Alteration in the composition of the microbial profiles has been suspected of having a role in carcinogenesis[1]. Indeed, recent studies suggested a correlation of particular bacterial profiles in HCC patients[74]. However, the contribution of GM to HCC pathogenesis is intricate: (1) A disturbed intestinal barrier brings a series of TLR ligands to the liver and activates inflammatory response; (2) *via* downregulation of hepatocyte apoptosis and upregulation of hepatic stellar cell proliferation, the TLR signaling pathways mediate hepatocarcinogenesis[102]; and (3) Finally, impaired immunosurveillance is associated with abnormal GM in HCC. Moreover, microbiota dysbiosis can be related to HCC pathogenesis by increasing oxidative stress, steatosis, and inflammatory response[103]. Additionally, the GM of HCC patients undergoing liver transplantation was compared to GM of patients who did not have HCC but had an analogous etiology of cirrhosis and MELD stage. Increased number of fecal *E. coli* HCC was associated with HCC[104]. Moreover, the presence of *Helicobacter spp*. in liver HCC tissue samples indicated intestinal translocation as a possible trigger of tumorigenesis[105]. Finally, the GM structure could theoretically predict reaction rates in liver cancer patients treated with particular immune checkpoint inhibitors[106], indicating the potential to harness the microbial flora for HCC immunotherapy[107].

***Role of fecal microbiota transplantation in viral hepatitis - future directions***

Different therapeutic approaches have been proposed to improve the health of patients with chronic viral hepatitis through the manipulation of GM composition, the modulation of immune signaling, and the production of metabolites[88,108]. It is found that some bacteria of the intestinal microbiota disappear from patients who received antibiotics within 3 mo[109]. It is speculated that region and eating habits might affect the flora of HBV positive patients[109]. Fecal microbiota transplantation (FMT) is considered to be a promising new treatment option for HBV and HCV infection, because of its ability to restore the GM dysbiosis[108].

Ren *et al*[110] reported a clinical trial of FMT for the treatment of HBeAg positive patients with chronic HBV with ongoing entecavir and tenofovir therapy. The results demonstrated that FMT induced HBeAg clearance in a significant number of patients that had persistent positive HBeAg even after long-term antiviral treatment. This result was especially encouraging for HBeAg positive patients who otherwise could not end oral antiviral treatment[110]. In addition, this trial provided evidence that FMT could be a beneficial treatment option for modulating GM in patients with chronic HBV. HBV carriers might be suitable donors for FMT as their GM composition seems to be more appropriate compared to a healthy population. The results of Yang *et al*[108] confirmed that HBV carriers have altered GM although they are asymptomatic. The high treatment FMT potential from HBV carriers comes from the evidence that they are able to keep a long-life balance with the virus without developing clinical symptoms. These data confirm the previous allegations that the change of the floral composition of HBV carriers may play an active role in the struggle between the human body and the virus[94,110]. Of course, more detailed studies are needed to verify these claims.

The use of probiotics in HBV positive patients showed to be beneficial and suggested that probiotic VSL#3 plays an important role in the management of HBV infection[111]. In addition, the use of probiotics in HCV-infected patients with cirrhosis is shown to be significantly beneficial[88]. In addition, it was suggested that during HCV infection, *L. acidophilus* and *Bifidobacterium spp*. can act as a supportive supplement with antiviral and antibacterial activities[112]. The results of Doskali *et al*[113] suggested that healthy GM increases the cytotoxic effects of NK cells against virally infected cells inhibiting the HCV replication. Finally, Yang *et al*[108] confirmed that some probiotics, such as lactic acid bacteria, may have a negative impact on the disease progression. The results of Yang *et al*[108] indicated that the intake of *Lactobacillus* should be cautious as these bacteria are negatively associated with environmental adaptation, energy metabolism, and the immune system and may have an influence on the progression of HBV infection[70,108].

**CONCLUSION**

This literature review provides evidence about an association between gut dysbiosis and the clinical course of both HBV and HCV chronic hepatitis. The evidences on humans seem to confirm the potential role of intestinal overgrowth of pathogenic bacteria and development of chronic viral hepatitis observed in animal-based studies. In addition, current clinical trials with different therapeutic strategies improved the present knowledge on the gut–liver axis, showing positive and encouraging results on how to overcome the battle with viral hepatitis. More studies on the liver-gut mechanistic interaction during HCV and HBV infection are still needed to unravel the cause-effect relationship between gut homeostasis and disease complications and to evaluate the efficacy of modulation of GM as a preventive strategy against chronic viral hepatitis progression and especially the development of hepatocarcinoma.

**ACKNOWLEDGEMENTS**

The authors thank Dr. Elisangela Miceli, PhD and Dr. Savannah Devente for English revisions.

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**Footnotes**

**Conflict-of-interest statement:** Authors declare no any conflict of interest.

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**Manuscript source:** Invited manuscript

**Peer-review started:** February 2, 2021

**First decision:** March 14, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Serbia

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

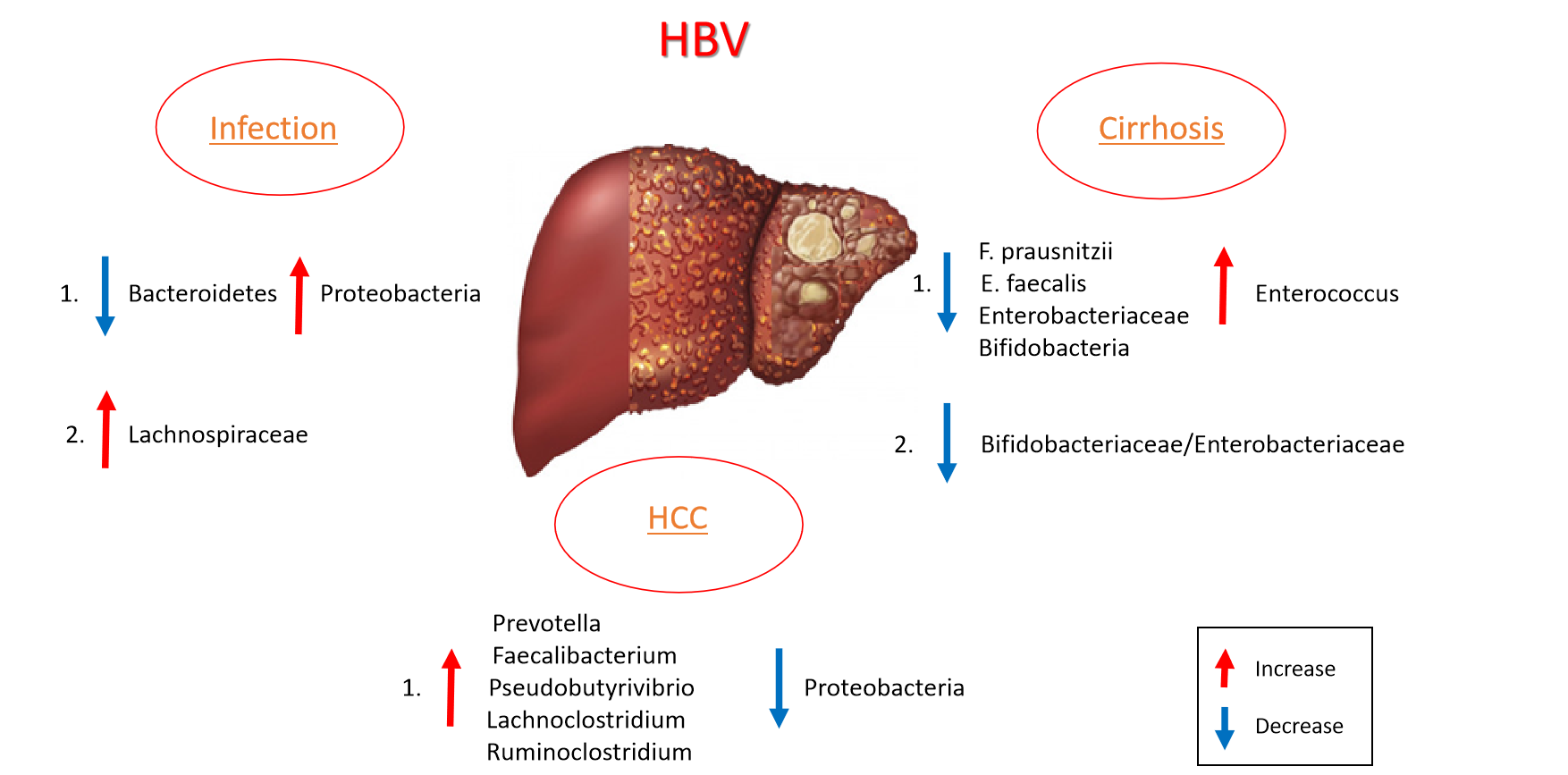
Grade C (Good): C

Grade D (Fair): 0

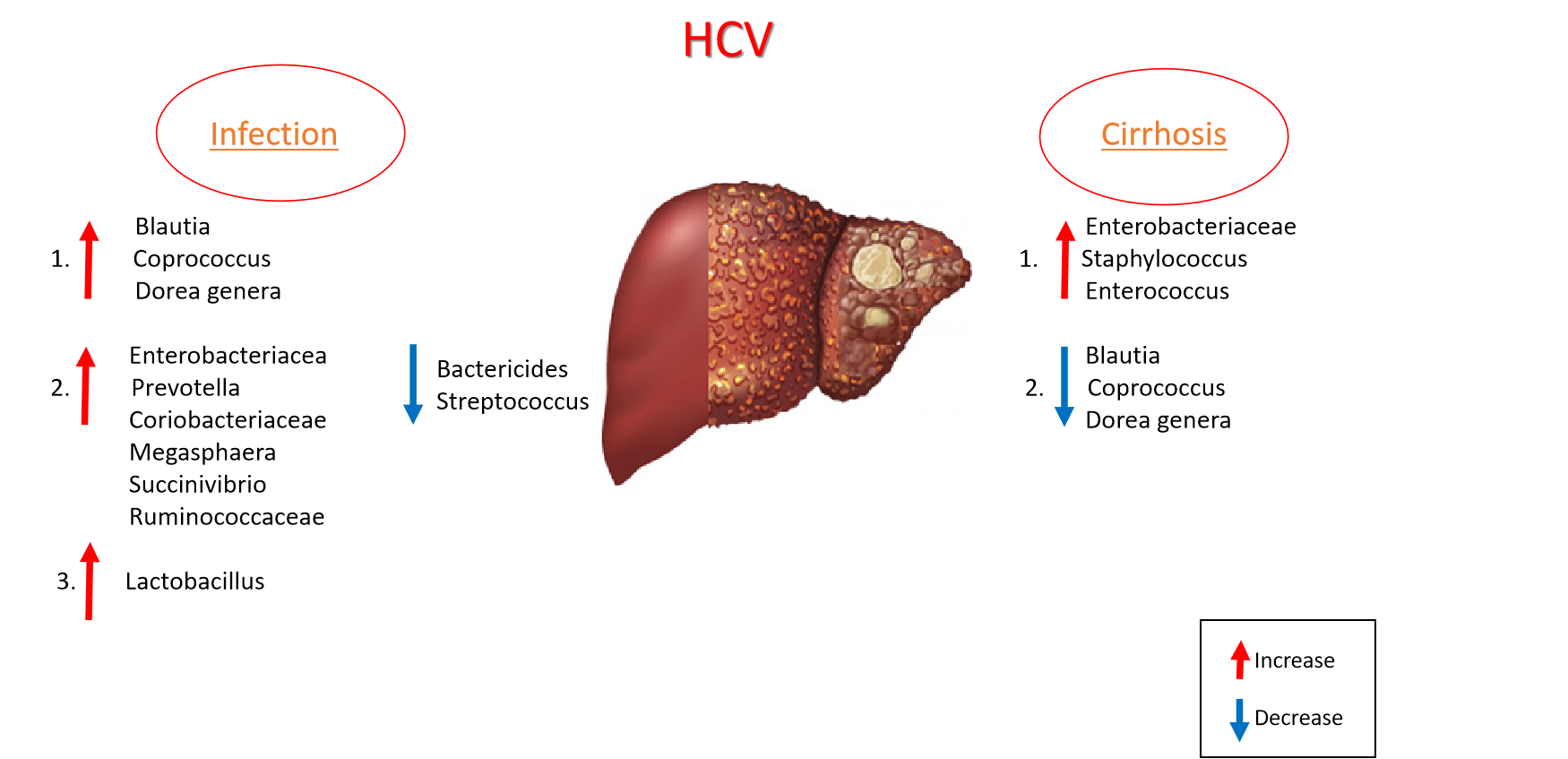
Grade E (Poor): 0

**P-Reviewer:** Zheng H **S-Editor:** Liu M **L-Editor: P-Editor:**

**Figure Legends**



**Figure 1 Altered microbiota during infection and cirrhosis in hepatitis B virus.** HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma.



**Figure 2 Altered microbiota during infection and cirrhosis in hepatitis C virus.** HCV: Hepatitis C virus.