ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2021 September 7; 27(33): 5460-5624

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 27 Number 33 September 7, 2021

THERAPEUTIC AND DIAGNOSTIC GUIDELINES

5460 Guidelines on postoperative magnetic resonance imaging in patients operated for cryptoglandular anal fistula: Experience from 2404 scans

Garg P, Kaur B, Yagnik VD, Dawka S, Menon GR

REVIEW

5474 Neutrophil extracellular traps in gastrointestinal cancer

Chu ZQ, Zhang KC, Chen L

5488 Microbiota and viral hepatitis: State of the art of a complex matter

Milosevic I, Russo E, Vujovic A, Barac A, Stevanovic O, Gitto S, Amedei A

5502 Clinical perspectives, assessment, and mechanisms of metabolic-associated fatty liver disease in patients with COVID-19

Campos-Murguía A, Román-Calleja BM, González-Regueiro JA, Hurtado-Díaz-de-León I, Solís-Ortega AA, Flores-García NC, García-Juárez I, Ruiz-Margáin A, Macías-Rodríguez RU

MINIREVIEWS

5520 Impact of COVID-19 on inflammatory bowel disease practice and perspectives for the future

Viganò C, Mulinacci G, Palermo A, Barisani D, Pirola L, Fichera M, Invernizzi P, Massironi S

5536 Surveillance for hepatocellular carcinoma in chronic viral hepatitis: Is it time to personalize it?

Demirtas CO, Brunetto MR

5555 Gut microbiota-derived metabolites as key mucosal barrier modulators in obesity

Wei YX, Zheng KY, Wang YG

ORIGINAL ARTICLE

Basic Study

5566 Adiponectin and the regulation of gastric content volume in the newborn rat

Wang H, Esemu-Ezewu P, Pan J, Ivanovska J, Gauda EB, Belik J

5575 Characterization of gut microbiome and metabolome in *Helicobacter pylori* patients in an underprivileged community in the United States

White B, Sterrett J, Grigoryan Z, Lally L, Heinze J, Alikhan H, Lowry C, Perez LJ, DeSipio J, Phadtare S

Retrospective Study

5595 Gastric cancer mortality related to direct radiographic and endoscopic screening: A retrospective study

Hagiwara H, Moki F, Yamashita Y, Saji K, Iesaki K, Suda H

5610 Radiomics for predicting perineural invasion status in rectal cancer

Li M, Jin YM, Zhang YC, Zhao YL, Huang CC, Liu SM, Song B

LETTER TO THE EDITOR

5622 Comment on "Diagnostic approach to faecal incontinence: What test and when to perform?"

Wang JT, Miao YD, Guan QL

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Güray Can, MD, Associate Professor, Chief, Department of Gastroenterology, Bolu İzzet Baysal Education and Research Hospital, Bolu Abant İzzet Baysal University, Gölköy Campus, Bolu 14030, Turkey. guraycan@ibu.edu.tr

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for *WJG* as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ze-Mao Gong*.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
September 7, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2021 September 7; 27(33): 5488-5501

DOI: 10.3748/wjg.v27.i33.5488

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

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

Ivana Milosevic, Edda Russo, Ankica Vujovic, Aleksandra Barac, Olja Stevanovic, Stefano Gitto, Amedeo Amedei

ORCID number: Ivana Milosevic 0000-0002-5014-8949; Edda Russo 0000-0003-3141-1091; Ankica Vujovic 0000-0001-9570-215X; Aleksandra Barac 0000-0002-0132-2277; Olja Stevanovic 0000-0001-9306-2128; Stefano Gitto 0000-0002-8042-6508; Amedeo Amedei 0000-0002-6797-9343.

Author contributions: Russo E and Milosevic I contributed equally; 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, and Russo E 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, and Amedei A acquired the funding; All authors critically revised the manuscript.

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

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in

Ivana Milosevic, Ankica Vujovic, Aleksandra Barac, Olja Stevanovic, Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia Faculty of Medicine, University of Belgrade, Belgrade 101801, Serbia

Edda Russo, Stefano Gitto, Amedeo Amedei, Department of Experimental and Clinical Medicine, University of Florence, Firenze 50100, Italy

Corresponding author: Ivana Milosevic, MD, Associate Professor, Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia Faculty of Medicine, University of Belgrade, Bul. Oslobodjenja 16, Belgrade 101801, Serbia. ivana.milosevic@med.bg.ac.rs

Abstract

Changes in 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 in 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 liver function and modulate the pathology of viral hepatitis. Recent studies showed that the gut microbiota produces various 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 the 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 remain unclear and not understood. In this review, we discuss the current findings of 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 virus; Hepatitis C virus; Liver diseases, Fecal transplantation

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

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

Received: February 2, 2021
Peer-review started: February 2, 2021
First decision: March 14, 2021
Revised: March 26, 2021
Accepted: July 21, 2021
Article in press: July 21, 2021
Published online: September 7, 2021

P-Reviewer: Zheng H
S-Editor: Liu M
L-Editor: Webster JR
P-Editor: Yuan YY

Core Tip: Changes within the gut microbiota have an impact on the mutual crosstalk between intestinal microbiota and the 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 remain unclear. We discuss recent studies to understand the role of gut microbiota.

Citation: Milosevic I, Russo E, 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; 27(33): 5488-5501
URL: https://www.wjgnet.com/1007-9327/full/v27/i33/5488.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i33.5488

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 the gut and brain to maintain intestinal homeostasis and host health[2,3]. However, gastrointestinal tract bacteria 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 the 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 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 due to increased production of 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 support the fact that GM dysbiosis helps the advancement of viral hepatitis infection[17]. During chronic viral hepatitis, the intestinal microbiota has a marked 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 the GM of patients with HBV and hepatitis C virus (HCV) infection and are correlated with the progression of liver disease[20-22].

This paper provides an overview of the state of the art of this complex matter. We discuss recent updates on 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 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 diseases, the pathogenesis and progression 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 light of this evidence, the 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 to an 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, *F. prausnitzii* was negatively correlated with CD163+ and CD45+ cells, while *Prevotella* was negatively correlated with CD20+ cells[31]. In addition, a GM signature was also demonstrated 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 *F. prausnitzii*, *Ruminococcus*, and *Coprococcus* abundance in comparison with healthy controls[27], while pediatric 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]. Although several reports have evaluated the GM, much less has been reported regarding the virome, defined as the total collection of viruses in and on the human body. More advanced NAFLD was associated with reduced viral (and relative bacteriophages) diversity[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]. However, very recent animal model research, 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 therapy changed the fecal microbiota in a placebo-controlled trial, but failed to change hepatic steatosis in subjects with NAFLD[38].

ALD

Several studies have been 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 *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 number 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 has demonstrated that bacterial overgrowth is central to disease progression[52]. These findings are also supported by mouse studies[53]. 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[54,55]. 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 in 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]. 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 to be 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 was inversely correlated with upregulated microbes in PBC patients, but was positively correlated with upregulated bacteria in healthy controls[59]. The 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 abundance 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 pro-inflammatory mechanism contributing to fibrosis and inflammation in cholangiocytes[68,69].

HBV infection

Liver failure and disease progression in patients with chronic HBV infection was found to be connected to GM dysbiosis in a large proportion[18,70]. There are differences in the composition of the intestinal flora between patients with HBV and HCV infection (Figures 1 and 2). Compared to healthy controls, patients with chronic HBV infection showed an 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 their progressive decline compared to healthy subjects[70]. In addition, Ren *et al*[74] documented that 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* a reduction in lipopolysaccharide (LPS) secretion and bacterial translocation[74,75]. The study by Lu *et al*[16] suggested 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 indicated that GM plays an important role in the progression of

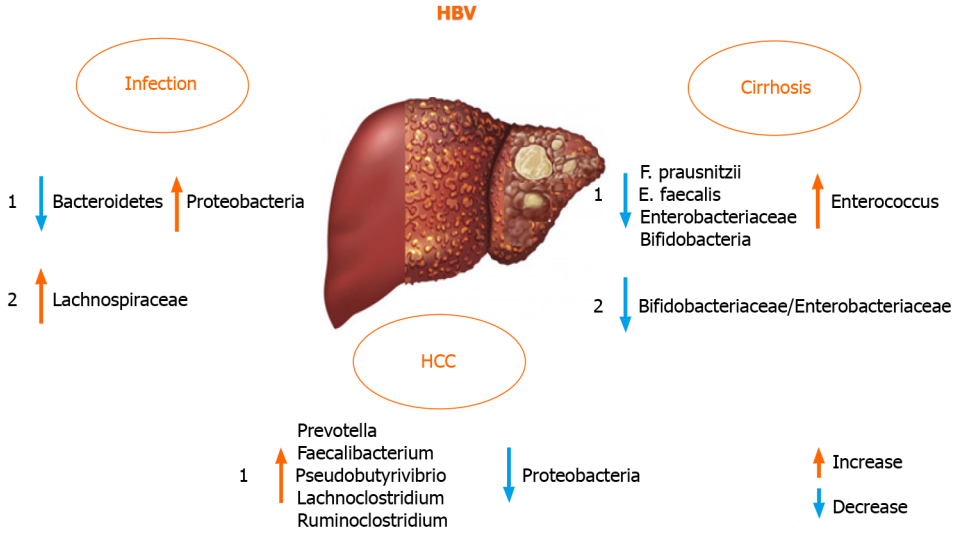

Figure 1 Differences in altered microbiota in patients with HBV during infection and cirrhosis. HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma.

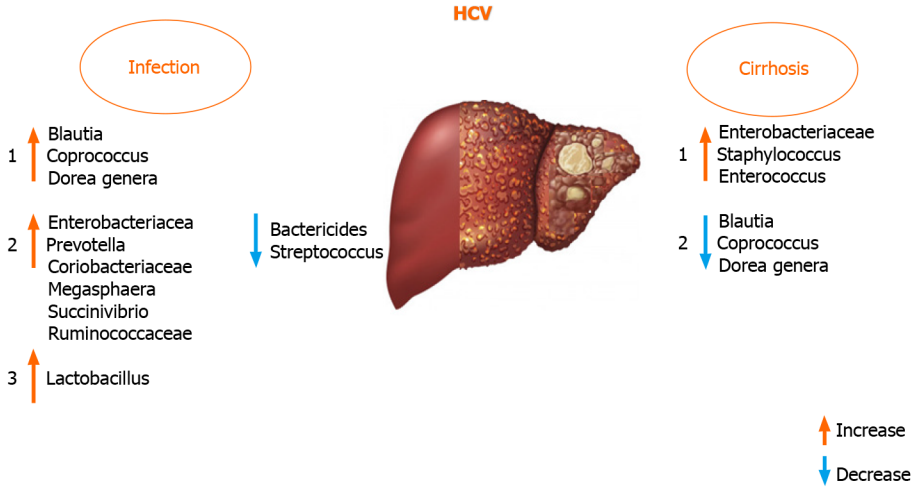

Figure 2 Differences in altered microbiota in patients with HCV during infection and cirrhosis. HCV: Hepatitis C virus.

HBV or non-HBV non-HCV related HCC. These findings were different from previous reports on 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 HBV positive and HBV negative patients in the study by Liu *et al*[70] is perhaps due 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 serum HBV-DNA and the 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 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 the B/E ratio is disturbed only in the GM of patients with cirrhosis. However, another study observed that the *Megasphaera* genus

of the Firmicutes phylum 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 negative patients[72]. These bacteria produce short-chain fatty acid as a by-product of lactate fermentation and butyrate. In Figure 1 we show the main microbiota alterations in HBV.

Recently, Wang *et al*[82] defined 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 these diseases[83]. It has been reported that the diagnostic model of one location may be not used in other locations, as 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 diagnostic potential of microbial markers should consider these geographic differences[79].

HCV infection

The liver-gut interaction controls GM homeostasis during HCV infection, which might be an ideal model to study the interaction between the GM and liver[18,80]. A 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 as in rotavirus infection[85]. Heidrich *et al*[86] found that progression of HCV infection is related to a reduced alpha diversity revealing that the relative abundance of phylotypes is associated with the stage of the disease. Additionally, Sultan *et al*[2] characterized the GM from a 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, the 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 the metabolism of cysteine and methionine and translation proteins was enriched compared to healthy controls[2]. The findings of Sultan *et al*[2] contradict previous literature that showed a decrease in GM diversity and changes within the abundance of some taxa such as *Prevotella*, *Ruminococcaceae*, *Enterobacteriacea*, and *Faecalibacterium* in patients with chronic HCV infection[2,15,86-88]. This could be due to many aspects such as 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 specific treatment has also received significant attention in GM research in other health disorders[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 bile acids, which is very important in GM metabolism[91]. Some pathogenic bacteria such as *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]. However, following DAA treatment, the 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 was not able to improve GM bacterial richness. However, partial restoration of 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 contributing to a definite GM profile. A lower abundance of *Akkermansia municiphila* was also 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 action of DAAs at this level. These results confirm those previously observed with prior 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 were increased in HCV positive patients, which is opposite to the lower presence of these bacteria observed in 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 the GM of healthy people has not been completely revealed.

An increased presence of *Lactobacillus* in HCV-infected patients was found in very few studies, although the study cohorts were not uniform (treatment-naïve and patients under a 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, as some probiotics are supported by bacterial strains belonging to this genus[96]. The main microbiota alterations in HCV infection are reported in Figure 2.

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 potential associations[15,75].

Cirrhosis

A recent study has shown that the GM has a 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 mucosa 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 were detected in the colon mucosa[97], serum[98], and saliva[99] of patients with cirrhosis. Interestingly, the improvement in 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 biomarkers. Intriguingly, a higher abundance of buccal-derived microflora was recorded in fecal specimens from 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 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 liver cirrhosis[101].

HCC

Alterations in the composition of the microbial profiles are suspected of having a role in carcinogenesis[1]. Indeed, recent studies suggested a correlation between 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 the 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 the inflammatory response[103]. Additionally, the GM of HCC patients undergoing liver transplantation was compared to the GM of patients who did not have HCC, but had an analogous etiology of cirrhosis and MELD stage. An increased number of fecal *E. coli* was associated with HCC[104]. Moreover, the presence of *Helicobacter spp*. in 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 was found that some bacteria of the intestinal microbiota disappeared in 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 a promising new treatment option for HBV and HCV infection, due to its ability to restore 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 stop 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 the 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 in flora 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 was shown 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 has been shown to be significantly beneficial[88]. 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 a healthy GM increases the cytotoxic effects of NK cells against viral infected cells; thus, inhibiting HCV replication. Finally, Yang *et al*[108] confirmed that some probiotics, such as lactic acid bacteria, may have a negative impact on 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 on the association between gut dysbiosis and the clinical course of both chronic HBV and HCV infection. The evidence in humans seems to confirm the potential role of intestinal overgrowth of pathogenic bacteria and the development of chronic viral hepatitis observed in animal-based studies. In addition, current clinical trials with different therapeutic strategies have 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 the 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.

REFERENCES

1 **Russo E**, Amedei A. The Role of the Microbiota in the Genesis of Gastrointestinal Cancers. In: Frontiers in Anti-Infective Drug Discovery. Bentham e Books: 1-44 [DOI: 10.2174/9781681085623118070003]

2 **Sultan S**, El-Mowafy M, Elgaml A, El-Mesery M, El Shabrawi A, Elegezy M, Hammami R, Mottawea W. Alterations of the Treatment-Naive Gut Microbiome in Newly Diagnosed Hepatitis C Virus Infection. *ACS Infect Dis* 2021; **7**: 1059-1068 [PMID: 33119247 DOI: 10.1021/acsinfecdis.0c00432]

3 **Milosevic I**, Vujovic A, Barac A, Djelic M, Korac M, Radovanovic Spurnic A, Gmizic I, Stevanovic O, Djordjevic V, Lekic N, Russo E, Amedei A. Gut-Liver Axis, Gut Microbiota, and Its Modulation in the Management of Liver Diseases: A Review of the Literature. *Int J Mol Sci* 2019; **20**: 395 [PMID: 30658519 DOI: 10.3390/ijms20020395]

4 **Qin J**, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012; **490**: 55-60 [PMID: 23023125 DOI: 10.1038/nature11450]

5 **Mottawea W**, Chiang CK, Mühlbauer M, Starr AE, Butcher J, Abujamel T, Deeke SA, Brandel A, Zhou H, Shokralla S, Hajibabaei M, Singleton R, Benchimol EI, Jobin C, Mack DR, Figeys D, Stintzi A. Altered intestinal microbiota-host mitochondria crosstalk in new onset Crohn's disease. *Nat Commun* 2016; **7**: 13419 [PMID: 27876802 DOI: 10.1038/ncomms13419]

6 **Distrutti E**, Monaldi L, Ricci P, Fiorucci S. Gut microbiota role in irritable bowel syndrome: New therapeutic strategies. *World J Gastroenterol* 2016; **22**: 2219-2241 [PMID: 26900286 DOI: 10.3748/wjg.v22.i7.2219]

7 **Ray K**. Gut microbiota: Adding weight to the microbiota's role in obesity--exposure to antibiotics early in life can lead to increased adiposity. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 615 [PMID: 22965425 DOI: 10.1038/nrgastro.2012.175]

8 **Arthur JC**, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, Campbell BJ, Abujamel T, Dogan B, Rogers AB, Rhodes JM, Stintzi A, Simpson KW, Hansen JJ, Keku TO, Fodor AA, Jobin C. Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science* 2012; **338**: 120-123 [PMID: 22903521 DOI: 10.1126/science.1224820]

9 **Valles-Colomer M**, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, Schiweck C, Kurilshikov A, Joossens M, Wijmenga C, Claes S, Van Oudenhove L, Zhernakova A, Vieira-Silva S, Raes J. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat Microbiol* 2019; **4**: 623-632 [PMID: 30718848 DOI: 10.1038/s41564-018-0337-x]

10 **Grąt M**, Wronka KM, Krasnodębski M, Masior Ł, Lewandowski Z, Kosińska I, Grąt K, Stypułkowski J, Rejowski S, Wasilewicz M, Gałęcka M, Szachta P, Krawczyk M. Profile of Gut Microbiota Associated With the Presence of Hepatocellular Cancer in Patients With Liver Cirrhosis. *Transplant Proc* 2016; **48**: 1687-1691 [PMID: 27496472 DOI: 10.1016/j.transproceed.2016.01.077]

11 **Brenner DA**, Paik YH, Schnabl B. Role of Gut Microbiota in Liver Disease. *J Clin Gastroenterol* 2015; **49** Suppl 1: S25-S27 [PMID: 26447960 DOI: 10.1097/MCG.0000000000000391]

12 **Giannelli V**, Di Gregorio V, Iebba V, Giusto M, Schippa S, Merli M, Thalheimer U. Microbiota and the gut-liver axis: bacterial translocation, inflammation and infection in cirrhosis. *World J Gastroenterol* 2014; **20**: 16795-16810 [PMID: 25492994 DOI: 10.3748/wjg.v20.i45.16795]

13 **Vassallo G**, Mirijello A, Ferrulli A, Antonelli M, Landolfi R, Gasbarrini A, Addolorato G. Review article: Alcohol and gut microbiota - the possible role of gut microbiota modulation in the treatment of alcoholic liver disease. *Aliment Pharmacol Ther* 2015; **41**: 917-927 [PMID: 25809237 DOI: 10.1111/apt.13164]

14 **Chassaing B**, Etienne-Mesmin L, Gewirtz AT. Microbiota-liver axis in hepatic disease. *Hepatology* 2014; **59**: 328-339 [PMID: 23703735 DOI: 10.1002/hep.26494]

15 **Qin N**, Yang F, Li A, Prifti E, Chen Y, Shao L, Guo J, Le Chatelier E, Yao J, Wu L, Zhou J, Ni S, Liu L, Pons N, Batto JM, Kennedy SP, Leonard P, Yuan C, Ding W, Hu X, Zheng B, Qian G, Xu W, Ehrlich SD, Zheng S, Li L. Alterations of the human gut microbiome in liver cirrhosis. *Nature* 2014; **513**: 59-64 [PMID: 25079328 DOI: 10.1038/nature13568]

16 **Lu H**, Wu Z, Xu W, Yang J, Chen Y, Li L. Intestinal microbiota was assessed in cirrhotic patients with hepatitis B virus infection. Intestinal microbiota of HBV cirrhotic patients. *Microb Ecol* 2011; **61**: 693-703 [PMID: 21286703 DOI: 10.1007/s00248-010-9801-8]

17 **Xu D**, Huang Y, Wang J. Gut microbiota modulate the immune effect against hepatitis B virus infection. *Eur J Clin Microbiol Infect Dis* 2015; **34**: 2139-2147 [PMID: 26272175 DOI: 10.1007/s10096-015-2464-0]

18 **Sehgal R**, Bedi O, Trehanpati N. Role of Microbiota in Pathogenesis and Management of Viral Hepatitis. *Front Cell Infect Microbiol* 2020; **10**: 341 [PMID: 32850467 DOI: 10.3389/fcimb.2020.00341]

19 **Bajaj JS**, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, Noble NA, Unser AB, Daita K, Fisher AR, Sikaroodi M, Gillevet PM. Altered profile of human gut microbiome is associated with cirrhosis and its complications. *J Hepatol* 2014; **60**: 940-947 [PMID: 24374295

DOI: 10.1016/j.jhep.2013.12.019]
20 **Chen Y**, Ji F, Guo J, Shi D, Fang D, Li L. Dysbiosis of small intestinal microbiota in liver cirrhosis and its association with etiology. *Sci Rep* 2016; **6**: 34055 [PMID: 27687977 DOI: 10.1038/srep34055]
21 **Mohamadkhani A**. On the potential role of intestinal microbial community in hepatocarcinogenesis in chronic hepatitis B. *Cancer Med* 2018; **7**: 3095-3100 [PMID: 29761927 DOI: 10.1002/cam4.1550]
22 **Cui L**, Morris A, Ghedin E. The human mycobiome in health and disease. *Genome Med* 2013; **5**: 63 [PMID: 23899327 DOI: 10.1186/gm467]
23 **Hartmann P**, Seebauer CT, Schnabl B. Alcoholic liver disease: the gut microbiome and liver cross talk. *Alcohol Clin Exp Res* 2015; **39**: 763-775 [PMID: 25872593 DOI: 10.1111/acer.12704]
24 **Wang R**, Tang R, Li B, Ma X, Schnabl B, Tilg H. Gut microbiome, liver immunology, and liver diseases. *Cell Mol Immunol* 2021; **18**: 4-17 [PMID: 33318628 DOI: 10.1038/s41423-020-00592-6]
25 **Zhu L**, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, Gill SR. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. *Hepatology* 2013; **57**: 601-609 [PMID: 23055155 DOI: 10.1002/hep.26093]
26 **Jiang W**, Wu N, Wang X, Chi Y, Zhang Y, Qiu X, Hu Y, Li J, Liu Y. Dysbiosis gut microbiota associated with inflammation and impaired mucosal immune function in intestine of humans with non-alcoholic fatty liver disease. *Sci Rep* 2015; **5**: 8096 [PMID: 25644696 DOI: 10.1038/srep08096]
27 **Da Silva HE**, Teterina A, Comelli EM, Taibi A, Arendt BM, Fischer SE, Lou W, Allard JP. Nonalcoholic fatty liver disease is associated with dysbiosis independent of body mass index and insulin resistance. *Sci Rep* 2018; **8**: 1466 [PMID: 29362454 DOI: 10.1038/s41598-018-19753-9]
28 **Alferink LJM**, Radjabzadeh D, Erler NS, Vojinovic D, Medina-Gomez C, Uitterlinden AG, de Knegt RJ, Amin N, Ikram MA, Janssen HLA, Kiefte-de Jong JC, Metselaar HJ, van Duijn CM, Kraaij R, Darwish Murad S. Microbiomics, Metabolomics, Predicted Metagenomics, and Hepatic Steatosis in a Population-Based Study of 1,355 Adults. *Hepatology* 2021; **73**: 968-982 [PMID: 32530501 DOI: 10.1002/hep.31417]
29 **Boursier J**, Mueller O, Barret M, Machado M, Fizanne L, Araujo-Perez F, Guy CD, Seed PC, Rawls JF, David LA, Hunault G, Oberti F, Calès P, Diehl AM. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. *Hepatology* 2016; **63**: 764-775 [PMID: 26600078 DOI: 10.1002/hep.28356]
30 **Raman M**, Ahmed I, Gillevet PM, Probert CS, Ratcliffe NM, Smith S, Greenwood R, Sikaroodi M, Lam V, Crotty P, Bailey J, Myers RP, Rioux KP. Fecal microbiome and volatile organic compound metabolome in obese humans with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2013; **11**: 868-75.e1 [PMID: 23454028 DOI: 10.1016/j.cgh.2013.02.015]
31 **Schwenger KJP**, Chen L, Chelliah A, Da Silva HE, Teterina A, Comelli EM, Taibi A, Arendt BM, Fischer S, Allard JP. Markers of activated inflammatory cells are associated with disease severity and intestinal microbiota in adults with nonalcoholic fatty liver disease. *Int J Mol Med* 2018; **42**: 2229-2237 [PMID: 30085339 DOI: 10.3892/ijmm.2018.3800]
32 **Loomba R**, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, Dulai PS, Caussy C, Bettencourt R, Highlander SK, Jones MB, Sirlin CB, Schnabl B, Brinkac L, Schork N, Chen CH, Brenner DA, Biggs W, Yooseph S, Venter JC, Nelson KE. Gut Microbiome-Based Metagenomic Signature for Non-invasive Detection of Advanced Fibrosis in Human Nonalcoholic Fatty Liver Disease. *Cell Metab* 2019; **30**: 607 [PMID: 31484056 DOI: 10.1016/j.cmet.2019.08.002]
33 **Cani PD**, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007; **56**: 1761-1772 [PMID: 17456850 DOI: 10.2337/db06-1491]
34 **Lang S**, Demir M, Martin A, Jiang L, Zhang X, Duan Y, Gao B, Wisplinghoff H, Kasper P, Roderburg C, Tacke F, Steffen HM, Goeser T, Abraldes JG, Tu XM, Loomba R, Stärkel P, Pride D, Fouts DE, Schnabl B. Intestinal Virome Signature Associated With Severity of Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2020; **159**: 1839-1852 [PMID: 32652145 DOI: 10.1053/j.gastro.2020.07.005]
35 **Caussy C**, Tripathi A, Humphrey G, Bassirian S, Singh S, Faulkner C, Bettencourt R, Rizo E, Richards L, Xu ZZ, Downes MR, Evans RM, Brenner DA, Sirlin CB, Knight R, Loomba R. A gut microbiome signature for cirrhosis due to nonalcoholic fatty liver disease. *Nat Commun* 2019; **10**: 1406 [PMID: 30926798 DOI: 10.1038/s41467-019-09455-9]
36 **Corbin KD**, Zeisel SH. Choline metabolism provides novel insights into nonalcoholic fatty liver disease and its progression. *Curr Opin Gastroenterol* 2012; **28**: 159-165 [PMID: 22134222 DOI: 10.1097/MOG.0b013e32834e7b4b]
37 **Song M**, Yuan F, Li X, Ma X, Yin X, Rouchka EC, Zhang X, Deng Z, Prough RA, McClain CJ. Analysis of sex differences in dietary copper-fructose interaction-induced alterations of gut microbial activity in relation to hepatic steatosis. *Biol Sex Differ* 2021; **12**: 3 [PMID: 33407877 DOI: 10.1186/s13293-020-00346-z]
38 **Scorletti E**, Afolabi PR, Miles EA, Smith DE, Almehmadi A, Alshathry A, Childs CE, Del Fabbro S, Bilson J, Moyses HE, Clough GF, Sethi JK, Patel J, Wright M, Breen DJ, Peebles C, Darekar A, Aspinall R, Fowell AJ, Dowman JK, Nobili V, Targher G, Delzenne NM, Bindels LB, Calder PC, Byrne CD. Synbiotics Alter Fecal Microbiomes, But Not Liver Fat or Fibrosis, in a Randomized Trial of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2020; **158**: 1597-1610

[PMID: 31987796 DOI: 10.1053/j.gastro.2020.01.031]
39 **Li F**, Duan K, Wang C, McClain C, Feng W. Probiotics and Alcoholic Liver Disease: Treatment and Potential Mechanisms. *Gastroenterol Res Pract* 2016; **2016**: 5491465 [PMID: 26839540 DOI: 10.1155/2016/5491465]
40 **Bull-Otterson L**, Feng W, Kirpich I, Wang Y, Qin X, Liu Y, Gobejishvili L, Joshi-Barve S, Ayvaz T, Petrosino J, Kong M, Barker D, McClain C, Barve S. Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of Lactobacillus rhamnosus GG treatment. *PLoS One* 2013; **8**: e53028 [PMID: 23326376 DOI: 10.1371/journal.pone.0053028]
41 **Tuomisto S**, Pessi T, Collin P, Vuento R, Aittoniemi J, Karhunen PJ. Changes in gut bacterial populations and their translocation into liver and ascites in alcoholic liver cirrhotics. *BMC Gastroenterol* 2014; **14**: 40 [PMID: 24564202 DOI: 10.1186/1471-230X-14-40]
42 **Bluemel S**, Williams B, Knight R, Schnabl B. Precision medicine in alcoholic and nonalcoholic fatty liver disease *via* modulating the gut microbiota. *Am J Physiol Gastrointest Liver Physiol* 2016; **311**: G1018-G1036 [PMID: 27686615 DOI: 10.1152/ajpgi.00245.2016]
43 **Davis BC**, Bajaj JS. The Human Gut Microbiome in Liver Diseases. *Semin Liver Dis* 2017; **37**: 128-140 [PMID: 28564721 DOI: 10.1055/s-0037-1602763]
44 **Kakiyama G**, Hylemon PB, Zhou H, Pandak WM, Heuman DM, Kang DJ, Takei H, Nittono H, Ridlon JM, Fuchs M, Gurley EC, Wang Y, Liu R, Sanyal AJ, Gillevet PM, Bajaj JS. Colonic inflammation and secondary bile acids in alcoholic cirrhosis. *Am J Physiol Gastrointest Liver Physiol* 2014; **306**: G929-G937 [PMID: 24699327 DOI: 10.1152/ajpgi.00315.2013]
45 **Kirpich IA**, Solovieva NV, Leikhter SN, Shidakova NA, Lebedeva OV, Sidorov PI, Bazhukova TA, Soloviev AG, Barve SS, McClain CJ, Cave M. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. *Alcohol* 2008; **42**: 675-682 [PMID: 19038698 DOI: 10.1016/j.alcohol.2008.08.006]
46 **Leclercq S**, Matamoros S, Cani PD, Neyrinck AM, Jamar F, Stärkel P, Windey K, Tremaroli V, Bäckhed F, Verbeke K, de Timary P, Delzenne NM. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. *Proc Natl Acad Sci USA* 2014; **111**: E4485-E4493 [PMID: 25288760 DOI: 10.1073/pnas.1415174111]
47 **Bode C**, Kolepke R, Schäfer K, Bode JC. Breath hydrogen excretion in patients with alcoholic liver disease--evidence of small intestinal bacterial overgrowth. *Z Gastroenterol* 1993; **31**: 3-7 [PMID: 8447153]
48 **Hauge T**, Persson J, Danielsson D. Mucosal bacterial growth in the upper gastrointestinal tract in alcoholics (heavy drinkers). *Digestion* 1997; **58**: 591-595 [PMID: 9438608 DOI: 10.1159/000201507]
49 **Morencos FC**, de las Heras Castaño G, Martín Ramos L, López Arias MJ, Ledesma F, Pons Romero F. Small bowel bacterial overgrowth in patients with alcoholic cirrhosis. *Dig Dis Sci* 1995; **40**: 1252-1256 [PMID: 7781442 DOI: 10.1007/BF02065533]
50 **Parlesak A**, Schäfer C, Schütz T, Bode JC, Bode C. Increased intestinal permeability to macromolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alcohol-induced liver disease. *J Hepatol* 2000; **32**: 742-747 [PMID: 10845660 DOI: 10.1016/s0168-8278(00)80242-1]
51 **Szabo G**. Gut-liver axis in alcoholic liver disease. *Gastroenterology* 2015; **148**: 30-36 [PMID: 25447847 DOI: 10.1053/j.gastro.2014.10.042]
52 **Mutlu EA**, Gillevet PM, Rangwala H, Sikaroodi M, Naqvi A, Engen PA, Kwasny M, Lau CK, Keshavarzian A. Colonic microbiome is altered in alcoholism. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G966-G978 [PMID: 22241860 DOI: 10.1152/ajpgi.00380.2011]
53 **Yan AW**, Fouts DE, Brandl J, Stärkel P, Torralba M, Schott E, Tsukamoto H, Nelson KE, Brenner DA, Schnabl B. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* 2011; **53**: 96-105 [PMID: 21254165 DOI: 10.1002/hep.24018]
54 **Llopis M**, Cassard AM, Wrzosek L, Boschat L, Bruneau A, Ferrere G, Puchois V, Martin JC, Lepage P, Le Roy T, Lefèvre L, Langelier B, Cailleux F, González-Castro AM, Rabot S, Gaudin F, Agostini H, Prévot S, Berrebi D, Ciocan D, Jousse C, Naveau S, Gérard P, Perlemuter G. Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease. *Gut* 2016; **65**: 830-839 [PMID: 26642859 DOI: 10.1136/gutjnl-2015-310585]
55 **Chen P**, Torralba M, Tan J, Embree M, Zengler K, Stärkel P, van Pijkeren JP, DePew J, Loomba R, Ho SB, Bajaj JS, Mutlu EA, Keshavarzian A, Tsukamoto H, Nelson KE, Fouts DE, Schnabl B. Supplementation of saturated long-chain fatty acids maintains intestinal eubiosis and reduces ethanol-induced liver injury in mice. *Gastroenterology* 2015; **148**: 203-214.e16 [PMID: 25239591 DOI: 10.1053/j.gastro.2014.09.014]
56 **Cresci GA**, Glueck B, McMullen MR, Xin W, Allende D, Nagy LE. Prophylactic tributyrin treatment mitigates chronic-binge ethanol-induced intestinal barrier and liver injury. *J Gastroenterol Hepatol* 2017; **32**: 1587-1597 [PMID: 28087985 DOI: 10.1111/jgh.13731]
57 **Tang R**, Wei Y, Li Y, Chen W, Chen H, Wang Q, Yang F, Miao Q, Xiao X, Zhang H, Lian M, Jiang X, Zhang J, Cao Q, Fan Z, Wu M, Qiu D, Fang JY, Ansari A, Gershwin ME, Ma X. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. *Gut* 2018; **67**: 534-541 [PMID: 28213609 DOI: 10.1136/gutjnl-2016-313332]
58 **Lv LX**, Fang DQ, Shi D, Chen DY, Yan R, Zhu YX, Chen YF, Shao L, Guo FF, Wu WR, Li A, Shi HY, Jiang XW, Jiang HY, Xiao YH, Zheng SS, Li LJ. Alterations and correlations of the gut microbiome, metabolism and immunity in patients with primary biliary cirrhosis. *Environ Microbiol*

2016; **18**: 2272-2286 [PMID: 27243236 DOI: 10.1111/1462-2920.13401]

59 **Chen W**, Wei Y, Xiong A, Li Y, Guan H, Wang Q, Miao Q, Bian Z, Xiao X, Lian M, Zhang J, Li B, Cao Q, Fan Z, Zhang W, Qiu D, Fang J, Gershwin ME, Yang L, Tang R, Ma X. Comprehensive Analysis of Serum and Fecal Bile Acid Profiles and Interaction with Gut Microbiota in Primary Biliary Cholangitis. *Clin Rev Allergy Immunol* 2020; **58**: 25-38 [PMID: 30900136 DOI: 10.1007/s12016-019-08731-2]

60 **Furukawa M**, Moriya K, Nakayama J, Inoue T, Momoda R, Kawaratani H, Namisaki T, Sato S, Douhara A, Kaji K, Kitade M, Shimozato N, Sawada Y, Saikawa S, Takaya H, Kitagawa K, Akahane T, Mitoro A, Yamao J, Tanaka Y, Yoshiji H. Gut dysbiosis associated with clinical prognosis of patients with primary biliary cholangitis. *Hepatol Res* 2020; **50**: 840-852 [PMID: 32346970 DOI: 10.1111/hepr.13509]

61 **Karlsen TH**. Primary sclerosing cholangitis: 50 years of a gut-liver relationship and still no love? *Gut* 2016; **65**: 1579-1581 [PMID: 27402486 DOI: 10.1136/gutjnl-2016-312137]

62 **Lemoinne S**, Kemgang A, Ben Belkacem K, Straube M, Jegou S, Corpechot C; Saint-Antoine IBD Network, Chazouillères O, Housset C, Sokol H. Fungi participate in the dysbiosis of gut microbiota in patients with primary sclerosing cholangitis. *Gut* 2020; **69**: 92-102 [PMID: 31003979 DOI: 10.1136/gutjnl-2018-317791]

63 **Kummen M**, Holm K, Anmarkrud JA, Nygård S, Vesterhus M, Høivik ML, Trøseid M, Marschall HU, Schrumpf E, Moum B, Røsjø H, Aukrust P, Karlsen TH, Hov JR. The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls. *Gut* 2017; **66**: 611-619 [PMID: 26887816 DOI: 10.1136/gutjnl-2015-310500]

64 **Bajer L**, Kverka M, Kostovcik M, Macinga P, Dvorak J, Stehlikova Z, Brezina J, Wohl P, Spicak J, Drastich P. Distinct gut microbiota profiles in patients with primary sclerosing cholangitis and ulcerative colitis. *World J Gastroenterol* 2017; **23**: 4548-4558 [PMID: 28740343 DOI: 10.3748/wjg.v23.i25.4548]

65 **Sabino J**, Vieira-Silva S, Machiels K, Joossens M, Falony G, Ballet V, Ferrante M, Van Assche G, Van der Merwe S, Vermeire S, Raes J. Primary sclerosing cholangitis is characterised by intestinal dysbiosis independent from IBD. *Gut* 2016; **65**: 1681-1689 [PMID: 27207975 DOI: 10.1136/gutjnl-2015-311004]

66 **Torres J**, Bao X, Goel A, Colombel JF, Pekow J, Jabri B, Williams KM, Castillo A, Odin JA, Meckel K, Fasihuddin F, Peter I, Itzkowitz S, Hu J. The features of mucosa-associated microbiota in primary sclerosing cholangitis. *Aliment Pharmacol Ther* 2016; **43**: 790-801 [PMID: 26857969 DOI: 10.1111/apt.13552]

67 **Rossen NG**, Fuentes S, Boonstra K, D'Haens GR, Heilig HG, Zoetendal EG, de Vos WM, Ponsioen CY. The mucosa-associated microbiota of PSC patients is characterized by low diversity and low abundance of uncultured Clostridiales II. *J Crohns Colitis* 2015; **9**: 342-348 [PMID: 25547975 DOI: 10.1093/ecco-jcc/jju023]

68 **Tabibian JH**, Talwalkar JA, Lindor KD. Role of the microbiota and antibiotics in primary sclerosing cholangitis. *Biomed Res Int* 2013; **2013**: 389537 [PMID: 24232746 DOI: 10.1155/2013/389537]

69 **Mattner J**. Impact of Microbes on the Pathogenesis of Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC). *Int J Mol Sci* 2016; **17**: 1864 [PMID: 27834858 DOI: 10.3390/ijms17111864]

70 **Liu Q**, Li F, Zhuang Y, Xu J, Wang J, Mao X, Zhang Y, Liu X. Alteration in gut microbiota associated with hepatitis B and non-hepatitis virus related hepatocellular carcinoma. *Gut Pathog* 2019; **11**: 1 [PMID: 30675188 DOI: 10.1186/s13099-018-0281-6]

71 **Deng YD**, Peng XB, Zhao RR, Ma CQ, Li JN, Yao LQ. The intestinal microbial community dissimilarity in hepatitis B virus-related liver cirrhosis patients with and without at alcohol consumption. *Gut Pathog* 2019; **11**: 58 [PMID: 31788031 DOI: 10.1186/s13099-019-0337-2]

72 **Yun Y**, Chang Y, Kim HN, Ryu S, Kwon MJ, Cho YK, Kim HL, Cheong HS, Joo EJ. Alterations of the Gut Microbiome in Chronic Hepatitis B Virus Infection Associated with Alanine Aminotransferase Level. *J Clin Med* 2019; **8**: 173 [PMID: 30717396 DOI: 10.3390/jcm8020173]

73 **Hamer HM**, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther* 2008; **27**: 104-119 [PMID: 17973645 DOI: 10.1111/j.1365-2036.2007.03562.x]

74 **Ren Z**, Li A, Jiang J, Zhou L, Yu Z, Lu H, Xie H, Chen X, Shao L, Zhang R, Xu S, Zhang H, Cui G, Sun R, Wen H, Lerut JP, Kan Q, Li L, Zheng S. Gut microbiome analysis as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma. *Gut* 2019; **68**: 1014-1023 [PMID: 30045880 DOI: 10.1136/gutjnl-2017-315084]

75 **Chen Y**, Yang F, Lu H, Wang B, Chen Y, Lei D, Wang Y, Zhu B, Li L. Characterization of fecal microbial communities in patients with liver cirrhosis. *Hepatology* 2011; **54**: 562-572 [PMID: 21574172 DOI: 10.1002/hep.24423]

76 **Wei X**, Yan X, Zou D, Yang Z, Wang X, Liu W, Wang S, Li X, Han J, Huang L, Yuan J. Abnormal fecal microbiota community and functions in patients with hepatitis B liver cirrhosis as revealed by a metagenomic approach. *BMC Gastroenterol* 2013; **13**: 175 [PMID: 24369878 DOI: 10.1186/1471-230X-13-175]

77 **Tsai KN**, Kuo CF, Ou JJ. Mechanisms of Hepatitis B Virus Persistence. *Trends Microbiol* 2018; **26**: 33-42 [PMID: 28823759 DOI: 10.1016/j.tim.2017.07.006]

78 **Betrapally NS**, Gillevet PM, Bajaj JS. Gut microbiome and liver disease. *Transl Res* 2017; **179**: 49-59 [PMID: 27477080 DOI: 10.1016/j.trsl.2016.07.005]

79 **Zhao Y**, Mao YF, Tang YS, Ni MZ, Liu QH, Wang Y, Feng Q, Peng JH, Hu YY. Altered oral microbiota in chronic hepatitis B patients with different tongue coatings. *World J Gastroenterol* 2018; **24**: 3448-3461 [PMID: 30122883 DOI: 10.3748/wjg.v24.i30.3448]

80 **Kanmani P**, Suganya K, Kim H. The Gut Microbiota: How Does It Influence the Development and Progression of Liver Diseases. *Biomedicines* 2020; **8**: 501 [PMID: 33207562 DOI: 10.3390/biomedicines8110501]

81 **Voukelatou P**, Vrettos I, Kalliakmanis A. Neurologic symptoms as the only manifestation of B_{12} deficiency in a young patient with normal hematocrit, MCV, peripheral blood smear and homocysteine levels. *Oxf Med Case Reports* 2016; **2016**: omw091 [PMID: 28031855 DOI: 10.1093/omcr/omw091]

82 **Wang WW**, Zhang Y, Huang XB, You N, Zheng L, Li J. Fecal microbiota transplantation prevents hepatic encephalopathy in rats with carbon tetrachloride-induced acute hepatic dysfunction. *World J Gastroenterol* 2017; **23**: 6983-6994 [PMID: 29097871 DOI: 10.3748/wjg.v23.i38.6983]

83 **Fasano A**. Intestinal permeability and its regulation by zonulin: diagnostic and therapeutic implications. *Clin Gastroenterol Hepatol* 2012; **10**: 1096-1100 [PMID: 22902773 DOI: 10.1016/j.cgh.2012.08.012]

84 **Heidrich B**, Steinmann E, Plumeier I, Kirschner J, Sollik L, Ziegert S, Engelmann M, Lehmann P, Manns MP, Pieper DH, Wedemeyer H. Frequent detection of HCV RNA and HCVcoreAg in stool of patients with chronic hepatitis C. *J Clin Virol* 2016; **80**: 1-7 [PMID: 27128354 DOI: 10.1016/j.jcv.2016.04.006]

85 **Kandasamy S**, Vlasova AN, Fischer D, Kumar A, Chattha KS, Rauf A, Shao L, Langel SN, Rajashekara G, Saif LJ. Differential Effects of Escherichia coli Nissle and Lactobacillus rhamnosus Strain GG on Human Rotavirus Binding, Infection, and B Cell Immunity. *J Immunol* 2016; **196**: 1780-1789 [PMID: 26800875 DOI: 10.4049/jimmunol.1501705]

86 **Heidrich B**, Vital M, Plumeier I, Döscher N, Kahl S, Kirschner J, Ziegert S, Solbach P, Lenzen H, Potthoff A, Manns MP, Wedemeyer H, Pieper DH. Intestinal microbiota in patients with chronic hepatitis C with and without cirrhosis compared with healthy controls. *Liver Int* 2018; **38**: 50-58 [PMID: 28561276 DOI: 10.1111/liv.13485]

87 **Inoue T**, Nakayama J, Moriya K, Kawaratani H, Momoda R, Ito K, Iio E, Nojiri S, Fujiwara K, Yoneda M, Yoshiji H, Tanaka Y. Gut Dysbiosis Associated With Hepatitis C Virus Infection. *Clin Infect Dis* 2018; **67**: 869-877 [PMID: 29718124 DOI: 10.1093/cid/ciy205]

88 **Preveden T**, Scarpellini E, Milić N, Luzza F, Abenavoli L. Gut microbiota changes and chronic hepatitis C virus infection. *Expert Rev Gastroenterol Hepatol* 2017; **11**: 813-819 [PMID: 28621554 DOI: 10.1080/17474124.2017.1343663]

89 **Gevers D**, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour M, Morgan XC, Kostic AD, Luo C, González A, McDonald D, Haberman Y, Walters T, Baker S, Rosh J, Stephens M, Heyman M, Markowitz J, Baldassano R, Griffiths A, Sylvester F, Mack D, Kim S, Crandall W, Hyams J, Huttenhower C, Knight R, Xavier RJ. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014; **15**: 382-392 [PMID: 24629344 DOI: 10.1016/j.chom.2014.02.005]

90 **Forslund K**, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, Prifti E, Vieira-Silva S, Gudmundsdottir V, Pedersen HK, Arumugam M, Kristiansen K, Voigt AY, Vestergaard H, Hercog R, Costea PI, Kultima JR, Li J, Jørgensen T, Levenez F, Dore J; MetaHIT consortium, Nielsen HB, Brunak S, Raes J, Hansen T, Wang J, Ehrlich SD, Bork P, Pedersen O. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature* 2015; **528**: 262-266 [PMID: 26633628 DOI: 10.1038/nature15766]

91 **Ponziani FR**, Putignani L, Paroni Sterbini F, Petito V, Picca A, Del Chierico F, Reddel S, Calvani R, Marzetti E, Sanguinetti M, Gasbarrini A, Pompili M. Influence of hepatitis C virus eradication with direct-acting antivirals on the gut microbiota in patients with cirrhosis. *Aliment Pharmacol Ther* 2018; **48**: 1301-1311 [PMID: 30345704 DOI: 10.1111/apt.15004]

92 **Pérez-Matute P**, Íñiguez M, Villanueva-Millán MJ, Recio-Fernández E, Vázquez AM, Sánchez SC, Morano LE, Oteo JA. Short-term effects of direct-acting antiviral agents on inflammation and gut microbiota in hepatitis C-infected patients. *Eur J Intern Med* 2019; **67**: 47-58 [PMID: 31221551 DOI: 10.1016/j.ejim.2019.06.005]

93 **Cani PD**, de Vos WM. Next-Generation Beneficial Microbes: The Case of *Akkermansia muciniphila* . *Front Microbiol* 2017; **8**: 1765 [PMID: 29018410 DOI: 10.3389/fmicb.2017.01765]

94 **Bajaj JS**, Kassam Z, Fagan A, Gavis EA, Liu E, Cox IJ, Kheradman R, Heuman D, Wang J, Gurry T, Williams R, Sikaroodi M, Fuchs M, Alm E, John B, Thacker LR, Riva A, Smith M, Taylor-Robinson SD, Gillevet PM. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. *Hepatology* 2017; **66**: 1727-1738 [PMID: 28586116 DOI: 10.1002/hep.29306]

95 **Aly AM**, Adel A, El-Gendy AO, Essam TM, Aziz RK. Gut microbiome alterations in patients with stage 4 hepatitis C. *Gut Pathog* 2016; **8**: 42 [PMID: 27625705 DOI: 10.1186/s13099-016-0124-2]

96 **Kwak DS**, Jun DW, Seo JG, Chung WS, Park SE, Lee KN, Khalid-Saeed W, Lee HL, Lee OY, Yoon BC, Choi HS. Short-term probiotic therapy alleviates small intestinal bacterial overgrowth, but does not improve intestinal permeability in chronic liver disease. *Eur J Gastroenterol Hepatol* 2014; **26**: 1353-1359 [PMID: 25244414 DOI: 10.1097/MEG.0000000000000214]

97 **Bajaj JS**, Hylemon PB, Ridlon JM, Heuman DM, Daita K, White MB, Monteith P, Noble NA, Sikaroodi M, Gillevet PM. Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G675-G685 [PMID: 22821944 DOI: 10.1152/ajpgi.00152.2012]

98 **Santiago A**, Pozuelo M, Poca M, Gely C, Nieto JC, Torras X, Román E, Campos D, Sarrabayrouse G, Vidal S, Alvarado-Tapias E, Guarner F, Soriano G, Manichanh C, Guarner C. Alteration of the serum microbiome composition in cirrhotic patients with ascites. *Sci Rep* 2016; **6**: 25001 [PMID: 27112233 DOI: 10.1038/srep25001]

99 **Bajaj JS**, Betrapally NS, Hylemon PB, Heuman DM, Daita K, White MB, Unser A, Thacker LR, Sanyal AJ, Kang DJ, Sikaroodi M, Gillevet PM. Salivary microbiota reflects changes in gut microbiota in cirrhosis with hepatic encephalopathy. *Hepatology* 2015; **62**: 1260-1271 [PMID: 25820757 DOI: 10.1002/hep.27819]

100 **Bajaj JS**, Vargas HE, Reddy KR, Lai JC, O'Leary JG, Tandon P, Wong F, Mitrani R, White MB, Kelly M, Fagan A, Patil R, Sait S, Sikaroodi M, Thacker LR, Gillevet PM. Association Between Intestinal Microbiota Collected at Hospital Admission and Outcomes of Patients With Cirrhosis. *Clin Gastroenterol Hepatol* 2019; **17**: 756-765 [PMID: 30036646 DOI: 10.1016/j.cgh.2018.07.022]

101 **Oh TG**, Kim SM, Caussy C, Fu T, Guo J, Bassirian S, Singh S, Madamba EV, Bettencourt R, Richards L, Yu RT, Atkins AR, Huan T, Brenner DA, Sirlin CB, Downes M, Evans RM, Loomba R. A Universal Gut-Microbiome-Derived Signature Predicts Cirrhosis. *Cell Metab* 2020; **32**: 901 [PMID: 33147487 DOI: 10.1016/j.cmet.2020.10.015]

102 **Dapito DH**, Mencin A, Gwak GY, Pradere JP, Jang MK, Mederacke I, Caviglia JM, Khiabanian H, Adeyemi A, Bataller R, Lefkowitch JH, Bower M, Friedman R, Sartor RB, Rabadan R, Schwabe RF. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. *Cancer Cell* 2012; **21**: 504-516 [PMID: 22516259 DOI: 10.1016/j.ccr.2012.02.007]

103 **Tripathi A**, Debelius J, Brenner DA, Karin M, Loomba R, Schnabl B, Knight R. The gut-liver axis and the intersection with the microbiome. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 397-411 [PMID: 29748586 DOI: 10.1038/s41575-018-0011-z]

104 **Sheng L**, Jena PK, Hu Y, Liu HX, Nagar N, Kalanetra KM, French SW, Mills DA, Wan YY. Hepatic inflammation caused by dysregulated bile acid synthesis is reversible by butyrate supplementation. *J Pathol* 2017; **243**: 431-441 [PMID: 28892150 DOI: 10.1002/path.4983]

105 **Krüttgen A**, Horz HP, Weber-Heynemann J, Vucur M, Trautwein C, Haase G, Luedde T, Roderburg C. Study on the association of Helicobacter species with viral hepatitis-induced hepatocellular carcinoma. *Gut Microbes* 2012; **3**: 228-233 [PMID: 22572832 DOI: 10.4161/gmic.19922]

106 **Routy B**, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquelot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria JC, Deutsch E, Loriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 2018; **359**: 91-97 [PMID: 29097494 DOI: 10.1126/science.aan3706]

107 **Russo E**, Nannini G, Dinu M, Pagliai G, Sofi F, Amedei A. Exploring the food-gut axis in immunotherapy response of cancer patients. *World J Gastroenterol* 2020; **26**: 4919-4932 [PMID: 32952339 DOI: 10.3748/wjg.v26.i33.4919]

108 **Yang XA**, Lv F, Wang R, Chang Y, Zhao Y, Cui X, Li H, Yang S, Li S, Zhao X, Mo Z, Yang F. Potential role of intestinal microflora in disease progression among patients with different stages of Hepatitis B. *Gut Pathog* 2020; **12**: 50 [PMID: 33117435 DOI: 10.1186/s13099-020-00391-4]

109 **David LA**, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014; **505**: 559-563 [PMID: 24336217 DOI: 10.1038/nature12820]

110 **Ren YD**, Ye ZS, Yang LZ, Jin LX, Wei WJ, Deng YY, Chen XX, Xiao CX, Yu XF, Xu HZ, Xu LZ, Tang YN, Zhou F, Wang XL, Chen MY, Chen LG, Hong MZ, Ren JL, Pan JS. Fecal microbiota transplantation induces hepatitis B virus e-antigen (HBeAg) clearance in patients with positive HBeAg after long-term antiviral therapy. *Hepatology* 2017; **65**: 1765-1768 [PMID: 28027582 DOI: 10.1002/hep.29008]

111 **Dhiman RK**, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, Khattri A, Malhotra S, Duseja A, Chawla YK. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. *Gastroenterology* 2014; **147**: 1327-1337 [PMID: 25450083 DOI: 10.1053/j.gastro.2014.08.031]

112 **Dore GJ**, Ward J, Thursz M. Hepatitis C disease burden and strategies to manage the burden (Guest Editors Mark Thursz, Gregory Dore and John Ward). *J Viral Hepat* 2014; **21** Suppl 1: 1-4 [PMID: 24713003 DOI: 10.1111/jvh.12253]

113 **Doskali M**, Tanaka Y, Ohira M, Ishiyama K, Tashiro H, Chayama K, Ohdan H. Possibility of adoptive immunotherapy with peripheral blood-derived $CD3^{-}CD56+$ and CD3+CD56+ cells for inducing antihepatocellular carcinoma and antihepatitis C virus activity. *J Immunother* 2011; **34**: 129-138 [PMID: 21304407 DOI: 10.1097/CJI.0b013e3182048c4e]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.