World Journal of Clinical Infectious Diseases

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Clin Infect Dis 2017 February 25; 7(1): 1-5

DOI: 10.5495/wjcid.v7.i1.1

ISSN 2220-3176 (online)

EDITORIAL

Is it enough to eliminate hepatitis C virus to reverse the damage caused by the infection?

Patricia Pérez-Matute, José A Oteo

Patricia Pérez-Matute, José A Oteo, Infectious Diseases Department, Center for Biomedical Research of La Rioja (CIBIR)-Hospital San Pedro, 26006 Logroño, La Rioja, Spain

Author contributions: Pérez-Matute P and Oteo JA contributed to this paper.

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

Manuscript source: Invited manuscript

Correspondence to: José A Oteo, MD, PhD, Head of the Infectious Disease Department, Center for Biomedical Research of La Rioja (CIBIR)-Hospital San Pedro, c/Piqueras, 98, 26006 Logroño, La Rioja, Spain. jaoteo@riojasalud.es
Telephone: +34-941-278871
Fax: +34-941-298667

Received: August 26, 2016
Peer-review started: August 27, 2016
First decision: October 28, 2016
Revised: November 18, 2016
Accepted: December 1, 2016
Article in press: December 2, 2016
Published online: February 25, 2017

Abstract

Hepatitis C virus (HCV) infection represents one of the major causes of chronic liver disease, hepatocellular carcinoma and morbidity/mortality worldwide. It is also a major burden to the healthcare systems. A complete elimination of the HCV from the body through treatment is now possible. However, HCV not only alters the hepatic function. Several extra-hepatic manifestations are present in HCV-infected patients, which increase the mortality rate. Liver and gut are closely associated in what is called the "gut-liver axis". A disrupted gut barrier leads to an increase in bacterial translocation and an activation of the mucosal immune system and secretion of inflammatory mediators that plays a key role in the progression of liver disease towards decompensated cirrhosis in HCV-infected patients. In addition, both qualitative and quantitative changes in the composition of the gut microbiota (GM) and states of chronic inflammation have been observed in patients with cirrhosis. Thus, a successful treatment of HCV infection should be also accompanied by a complete restoration of GM composition in order to avoid activation of the mucosal immune system, persistent inflammation and the development of long-term complications. Evaluation of GM composition after treatment could be of interest as a reliable indicator of the total or partial cure of these patients. However, studies focused on microbiota composition after HCV eradication from the body are lacking, which opens unique opportunities to deeply explore and investigate this exciting field.

Key words: Hepatitis C infection; Inflammation; Virus eradication; Direct-acting antivirals; Gut microbiota

Core tip: Hepatitis C infection represents one of the major causes of chronic liver disease, hepatocellular carcinoma and morbidity/mortality worldwide. A complete elimination of the hepatitis C virus (HCV) from the body through treatment is now possible. However, HCV not only alters the hepatic function. In fact, changes in gut microbiota composition (GM) and gut barrier that leads to an increased bacterial translocation and inflammation have also been observed. Thus, a successful treatment

of HCV infection should be accompanied by a complete restoration of GM and inflammation. Studies focused on GM after HCV eradication are lacking, which opens unique opportunities to deeply explore this exciting field.

Pérez-Matute P, Oteo JA. Is it enough to eliminate hepatitis C virus to reverse the damage caused by the infection? *World J Clin Infect Dis* 2017; 7(1): 1-5 Available from: URL: http://www.wjgnet.com/2220-3176/full/v7/i1/1.htm DOI: http://dx.doi.org/10.5495/wjcid.v7.i1.1

Infection with hepatitis C virus (HCV) is one of the major causes of liver damage and morbidity/mortality worldwide[1]. The spectrum of this disease is quite variable, ranging from acute hepatitis to cirrhosis and hepatocellular carcinoma (HCC). In fact, HCV is considered the most important risk factor for the development of this type of cancer[2], one of the more common cancers in the general population that has substantially increased in recent years.

HCV infection is a major burden to the healthcare systems, as it is the most frequent indication for virus-related liver transplantation in the western world[3]. In addition, patients diagnosed with HCV showed increased morbidity, with higher hospital admission rates[4] and with mortality rates three times higher than that of the general population[5]. In a recent meta-analysis, the number of people with anti-HCV antibodies has been estimated at 185 million in 2005 (2.8% of the human population), with an estimation of 130-170 million people chronically infected[6]. Overall, between 300000-700000 people die every year due to liver diseases associated with HCV-infection[7,8].

Liver is, by far, the most affected organ, but HCV infection is definitely not a liver-limited disease. Actually, HCV infection has been associated with other extra-hepatic manifestations that include thyroid diseases, renal and cardiovascular diseases, eye and skin diseases, lymphomas, mixed cryoglobulinemia, dyslipidemia, diabetes and central nervous system diseases (brilliantly reviewed by several authors)[9-13]. In fact, up to 74% of HCV-infected patients experienced some form of these extra-hepatic manifestations[14]. Therefore, HCV infection showed a higher mortality rate due to the presence of these extra-hepatic complications[15-17]. Several studies have also suggested that HCV may infect other tissues apart from liver. Thus, HCV has been found in peripheral blood mononuclear cell[18,19], kidney, heart, pancreas, and in intestine[20,21]. The infected extra-hepatic tissues might act as potential reservoirs for HCV, and could play a role in both HCV persistence and reactivation of infection but could also contribute to the aforementioned extra-hepatic manifestations associated with HCV infection. Despite the fact that a growing interest has recently emerged concerning the extra-hepatic manifestations of chronic HCV infection, as demonstrated by the increasing number of reviews recently published, there is no scientific evidence that could demonstrate an association between the presence of the virus in other tissues different from liver and the extra-hepatic complications. Therefore, this issue deserves further investigation.

One area of investigation that has been the focus of much recent interest in the last years is the role of intestinal microbiota in health and disease[22]. Microbiota is defined as the collective microbial community inhabiting a specific environment, including bacteria, archaea, viruses, and some unicellular eukaryotes. Microbiota, its evolutive dynamics and influence on host through its protective, trophic and metabolic actions, has a key role in health and opens unique opportunities for the identification of new markers of the physiopathological state of each individual. Recent studies have demonstrated that changes in gut microbiota (GM) contribute to an increased intestinal permeability and, consequently, increased bacterial translocation and endotoxemia, which triggers inflammation and several deleterious actions[23]. In this sense, changes in GM composition is associated with plenty disorders, including liver disorders[22,24-27].

The effects of GM are not limited to the intestine (gut). Indeed, the gut and the liver are closely associated and there is continuous bidirectional communication between these two organs through the bile, hormones and other products of digestion and absorption. This association is known as the "gut-liver axis" and includes transfer of molecules associated with the gut microbiome to the liver and on the other way round[24,28]. Therefore, it is plausible that the composition of the intestinal microbiota could have direct and indirect effects on the function and physiology of the liver and possibly liver disease progression[29-31]. In addition, it has also been suggested that several liver products, such as bile acids, could directly influence the GM composition[30].

A disrupted gut barrier leads to an increase in bacterial translocation and to an activation of the mucosal immune system and secretion of inflammatory mediators that has a key role in the development of several liver disorders associated with HCV-infection, especially in the progression of liver disease towards decompensated cirrhosis in both HCV-mono infected and HCV/HIV co-infected patients[32-36]. In this context, the study carried out by Sandler *et al*[37] (2011) in HCV-infected patients showed that LPS-induced activation of both circulating monocytes and resident Kupffer cells was associated with severe hepatic fibrosis and failure to respond to therapy (based on interferon or pegylated interferon with or without ribavirin) and predicts progression to end-stage liver disease independent of the degree of fibrosis. In addition, several studies have demonstrated both qualitative and quantitative changes in the composition of the GM in patients with cirrhosis (summarized by Betrapally *et al*[38]). More specifically, the alteration in GM of cirrhotic patients (with and without HCV infection) is characterized by an overgrowth of potentially pathogenic bacteria (*i.e.,* gram negative species) and a decrease in autochthonous familiae[24]. Significant differences in the microbiota community and metabolic potential have

also been detected in the fecal microbiota of patients with hepatitis B liver cirrhosis[39]. Therefore, preservation of GM composition - through the usage of different approaches such as probiotics, prebiotics, *etc.,* arises as a promising tool to prevent and/or to treat the development of these liver disorders[40-44]. However, studies focused on microbiota composition of a large population of HCV patients (over the entire disease spectrum) are lacking and only studies concerning cirrhosis and HCC independently of their etiology can be found.

On the other hand, it is important to mention that one of the main objectives of health professionals when treating infectious diseases is to eliminate the pathogenic microorganism responsible for such disorder. To achieve this, physicians are provided with a large arsenal of antibiotics, antivirals, antiretroviral, *etc*., that have appeared in the last decades thanks to the spectacular progress of scientific research. In the context of HCV-infection, the last five years have been crucial in the fight against this infection. A few years ago, physicians only had therapies based on the combination of weekly pegylated interferon-α and daily doses of ribavirin to treat this infection. The efficacy of these therapies was not higher than 50%, and their mechanism of action was not direct against the virus, but was based on enhancing the immune system. In 2011, the arrival of first-generation direct-acting antivirals has shown successful rates of virus elimination from the body in more than 75% of the cases. Unlike the previous therapies, these new regimens cause fewer side effects, they do not require monitoring and most of them are pangenotypic. These therapies are also simpler and require a shorter duration. Thus, and despite the fact that there is not an effective vaccine yet, this could be the beginning of the end of hepatitis C disease[1,45]. However, a complete cure of HCV-infection requires not only the elimination of the virus from the body, but also would imply an improvement in liver and in the extra-hepatic manifestations. In this sense, the study from Innes *et al*[46] (2015), demonstrated a clear association between achievement of HCV cure [as evidenced by sustained viral response (SVR)] and a decrease in both liver-related and all-cause mortality. A large study of HCV-infected patients in the Veteran's Administration database also demonstrated that non-liver-related mortality was significantly reduced among patients who achieved SVR who had comorbidities that included coronary artery disease, diabetes, and hypertension. It was suggested that decreased chronic inflammation associated with HCV was a key factor in mortality decline[47,48]. It is important to highlight that changes in microbiota composition are present in states of chronic inflammation. Thus, a successful treatment of HCV infection should be also accompanied by a complete restoration of GM composition in order to avoid activation of the mucosal immune system, persistent inflammation and the development of different long-term complications. Thus, evaluation of GM composition after treatment could be of interest as a reliable indicator of the total or partial cure of these patients. Only a very preliminary study has been recently published in this regard[49]. It demonstrated that the pro-inflammatory state and the changes observed in GM composition of HCV-infected patients with cirrhosis were not improved regardless of at least one year of SVR. This persistent dysbiosis could contribute towards varying rates of improvement after HCV eradication in cirrhosis. However, what happen in HCV-infected patients with a lower degree of fibrosis/liver damage? Could HCV have a direct effect on GM composition since the presence of this virus has been demonstrated in intestine? or the changes observed in GM are only secondary to liver damage induced by the virus? These are only a few questions that arise in this exciting field and that deserve further investigation. A deep evaluation of the short, medium and long-term consequences of the new HCV treatments is needed, specially focused on the effects on GM composition, bacterial translocation and inflammation.

REFERENCES

1 **Barth H**. Hepatitis C virus: Is it time to say goodbye yet? Perspectives and challenges for the next decade. *World J Hepatol* 2015; **7**: 725-737 [PMID: 25914773 DOI: 10.4254/wjh.v7.i5.725]

2 **Hatzakis A**, Wait S, Bruix J, Buti M, Carballo M, Cavaleri M, Colombo M, Delarocque-Astagneau E, Dusheiko G, Esmat G, Esteban R, Goldberg D, Gore C, Lok AS, Manns M, Marcellin P, Papatheodoridis G, Peterle A, Prati D, Piorkowsky N, Rizzetto M, Roudot-Thoraval F, Soriano V, Thomas HC, Thursz M, Valla D, van Damme P, Veldhuijzen IK, Wedemeyer H, Wiessing L, Zanetti AR, Janssen HL. The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference*. *J Viral Hepat* 2011; **18** Suppl 1: 1-16 [PMID: 21824223 DOI: 10.1111/j.1365-2893.2011.01499.x]

3 **Hajarizadeh B**, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 553-562 [PMID: 23817321 DOI: 10.1038/nrgastro.2013.107]

4 **McDonald SA**, Hutchinson SJ, Bird SM, Mills PR, Hayes P, Dillon JF, Goldberg DJ. Excess morbidity in the hepatitis C-diagnosed population in Scotland, 1991-2006. *Epidemiol Infect* 2011; **139**: 344-353 [PMID: 20587118 DOI: 10.1017/S0950268810001421]

5 **Neal KR**, Ramsay S, Thomson BJ, Irving WL. Excess mortality rates in a cohort of patients infected with the hepatitis C virus: a prospective study. *Gut* 2007; **56**: 1098-1104 [PMID: 17344277 DOI: 10.1136/gut.2006.113217]

6 **Mohd Hanafiah K**, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; **57**: 1333-1342 [PMID: 23172780 DOI: 10.1002/hep.26141]

7 **Lozano R**, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton

LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095-2128 [PMID: 23245604 DOI: 10.1016/S0140-6736(12)61728-0]

8 **Muñoz-Gámez JA**, Salmerón J. Prevalence of hepatitis B and C in Spain - further data are needed. *Rev Esp Enferm Dig* 2013; **105**: 245-248 [PMID: 23971654 DOI: 10.4321/S1130-01082013000500001]

9 **Alvares-da-Silva MR**, Wedemeyer H, Cortez-Pinto H, Marques Souza de Oliveira CP. Hepatitis C and metabolic disorders: genetics, mechanism, and therapies (clinical and experimental). *Int J Hepatol* 2012; **2012**: 937202 [PMID: 23304531 DOI: 10.1155/2012/937202]

10 **Cacoub P**, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D. Extrahepatic manifestations of chronic hepatitis C virus infection. *Ther Adv Infect Dis* 2016; **3**: 3-14 [PMID: 26862398 DOI: 10.1177/2049936115585942]

11 **Gill K**, Ghazinian H, Manch R, Gish R. Hepatitis C virus as a systemic disease: reaching beyond the liver. *Hepatol Int* 2016; **10**: 415-423 [PMID: 26660706 DOI: 10.1007/s12072-015-9684-3]

12 **Sherman AC**, Sherman KE. Extrahepatic manifestations of hepatitis C infection: navigating CHASM. *Curr HIV/AIDS Rep* 2015; **12**: 353-361 [PMID: 26208812 DOI: 10.1007/s11904-015-0274-8]

13 **Tang L**, Marcell L, Kottilil S. Systemic manifestations of hepatitis C infection. *Infect Agent Cancer* 2016; **11**: 29 [PMID: 27222662 DOI: 10.1186/s13027-016-0076-7]

14 **Cacoub P**, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, Opolon P. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. *Arthritis Rheum* 1999; **42**: 2204-2212 [PMID: 10524695 DOI: 10.1002/1529-0131(199910)42:10<2204::AID-ANR24>3.0.CO;2-D]

15 **Lee MH**, Yang HI, Lu SN, Jen CL, You SL, Wang LY, Wang CH, Chen WJ, Chen CJ. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis* 2012; **206**: 469-477 [PMID: 22811301 DOI: 10.1093/infdis/jis385]

16 **Maasoumy B**, Wedemeyer H. Natural history of acute and chronic hepatitis C. *Best Pract Res Clin Gastroenterol* 2012; **26**: 401-412 [PMID: 23199500 DOI: 10.1016/j.bpg.2012.09.009]

17 **Omland LH**, Jepsen P, Krarup H, Schønning K, Lind B, Kromann-Andersen H, Homburg KM, Christensen PB, Sørensen HT, Obel N. Increased mortality among persons infected with hepatitis C virus. *Clin Gastroenterol Hepatol* 2011; **9**: 71-78 [PMID: 20888437 DOI: 10.1016/j.cgh.2010.09.014]

18 **Mahran MZ**, Elalim AA, Abbas A. Peripheral blood mononuclear cells serve as a possible extrahepatic site for hepatitis C virus replication. *Egypt J Immunol* 2009; **16**: 63-70 [PMID: 22059354]

19 **Natarajan V**, Kottilil S, Hazen A, Adelsberger J, Murphy AA, Polis MA, Kovacs JA. HCV in peripheral blood mononuclear cells are predominantly carried on the surface of cells in HIV/HCV co-infected individuals. *J Med Virol* 2010; **82**: 2032-2037 [PMID: 20981790 DOI: 10.1002/jmv.21906]

20 **Yan FM**, Chen AS, Hao F, Zhao XP, Gu CH, Zhao LB, Yang DL, Hao LJ. Hepatitis C virus may infect extrahepatic tissues in patients with hepatitis C. *World J Gastroenterol* 2000; **6**: 805-811 [PMID: 11819700 DOI: 10.3748/wjg.v6.i6.805]

21 **Deforges S**, Evlashev A, Perret M, Sodoyer M, Pouzol S, Scoazec JY, Bonnaud B, Diaz O, Paranhos-Baccalà G, Lotteau V, André P. Expression of hepatitis C virus proteins in epithelial intestinal cells in vivo. *J Gen Virol* 2004; **85**: 2515-2523 [PMID: 15302945 DOI: 10.1099/vir.0.80071-0]

22 **Villanueva-Millán MJ**, Pérez-Matute P, Oteo JA. Gut microbiota: a key player in health and disease. A review focused on obesity. *J Physiol Biochem* 2015; **71**: 509-525 [PMID: 25749935 DOI: 10.1007/s13105-015-0390-3]

23 **Cani PD**, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; **57**: 1470-1481 [PMID: 18305141 DOI: 10.2337/db07-1403]

24 **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]

25 **Brandl K**, Schnabl B. Is intestinal inflammation linking dysbiosis to gut barrier dysfunction during liver disease? *Expert Rev Gastroenterol Hepatol* 2015; **9**: 1069-1076 [PMID: 26088524 DOI: 10.1586/17474124.2015.1057122]

26 **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]

27 **Wieland A**, Frank DN, Harnke B, Bambha K. Systematic review: microbial dysbiosis and nonalcoholic fatty liver disease. *Aliment Pharmacol Ther* 2015; **42**: 1051-1063 [PMID: 26304302 DOI: 10.1111/apt.13376]

28 **Paolella G**, Mandato C, Pierri L, Poeta M, Di Stasi M, Vajro P. Gut-liver axis and probiotics: their role in non-alcoholic fatty liver disease. *World J Gastroenterol* 2014; **20**: 15518-15531 [PMID: 25400436 DOI: 10.3748/wjg.v20.i42.15518]

29 **Kakiyama G**, Pandak WM, Gillevet PM, Hylemon PB, Heuman DM, Daita K, Takei H, Muto A, Nittono H, Ridlon JM, White MB, Noble NA, Monteith P, Fuchs M, Thacker LR, Sikaroodi M, Bajaj JS. Modulation of the fecal bile acid profile by gut microbiota in cirrhosis. *J Hepatol* 2013; **58**: 949-955 [PMID: 23333527 DOI: 10.1016/j.jhep.2013.01.003]

30 **Nie YF**, Hu J, Yan XH. Cross-talk between bile acids and intestinal microbiota in host metabolism and health. *J Zhejiang Univ Sci B* 2015; **16**: 436-446 [PMID: 26055905 DOI: 10.1631/jzus.B1400327]

31 **Visschers RG**, Luyer MD, Schaap FG, Olde Damink SW, Soeters PB. The gut-liver axis. *Curr Opin Clin Nutr Metab Care* 2013; **16**: 576-581 [PMID: 23873346 DOI: 10.1097/MCO.0b013e32836410a4]

32 **French AL**, Evans CT, Agniel DM, Cohen MH, Peters M, Landay AL, Desai SN. Microbial translocation and liver disease progression in women coinfected with HIV and hepatitis C virus. *J Infect Dis* 2013; **208**: 679-689 [PMID: 23687224 DOI: 10.1093/infdis/jit225]

33 **Munteanu D**, Negru A, Radulescu M, Mihailescu R, Arama SS, Arama V. Evaluation of bacterial translocation in patients with chronic HCV infection. *Rom J Intern Med* 2014; **52**: 91-96 [PMID: 25338345]

34 **Sacchi P**, Cima S, Corbella M, Comolli G, Chiesa A, Baldanti F, Klersy C, Novati S, Mulatto P, Mariconti M, Bazzocchi C, Puoti M, Pagani L, Filice G, Bruno R. Liver fibrosis, microbial translocation and immune activation markers in HIV and HCV infections and in HIV/HCV co-infection. *Dig Liver Dis* 2015; **47**: 218-225 [PMID: 25544657 DOI: 10.1016/j.dld.2014.11.012]

35 **Roderburg C**, Luedde T. The role of the gut microbiome in the development and progression of liver cirrhosis and hepatocellular carcinoma. *Gut Microbes* 2014; **5**: 441-445 [PMID: 25006881 DOI: 10.4161/gmic.29599]

36 **Márquez M**, Fernández Gutiérrez del Álamo C, Girón-González JA. Gut epithelial barrier dysfunction in human immunodeficiency

virus-hepatitis C virus coinfected patients: Influence on innate and acquired immunity. *World J Gastroenterol* 2016; **22**: 1433-1448 [PMID: 26819512 DOI: 10.3748/wjg.v22.i4.1433]

37 **Sandler NG**, Koh C, Roque A, Eccleston JL, Siegel RB, Demino M, Kleiner DE, Deeks SG, Liang TJ, Heller T, Douek DC. Host response to translocated microbial products predicts outcomes of patients with HBV or HCV infection. *Gastroenterology* 2011; **141**: 1220-1230, 1230e1-e3 [PMID: 21726511 DOI: 10.1053/j.gastro.2011.06.063]

38 **Betrapally NS**, Gillevet PM, Bajaj JS. Gut microbiome and liver disease. *Transl Res* 2016 Jul 15; **179**: 49-59 [PMID: 27477080 DOI: 10.1016/j.trsl.2016.07.005]

39 **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]

40 **Adawi D**, Ahrné S, Molin G. Effects of different probiotic strains of Lactobacillus and Bifidobacterium on bacterial translocation and liver injury in an acute liver injury model. *Int J Food Microbiol* 2001; **70**: 213-220 [PMID: 11764187 DOI: 10.1016/S0168-1605(01)00550-5]

41 **Bajaj JS**, Heuman DM, Hylemon PB, Sanyal AJ, Puri P, Sterling RK, Luketic V, Stravitz RT, Siddiqui MS, Fuchs M, Thacker LR, Wade JB, Daita K, Sistrun S, White MB, Noble NA, Thorpe C, Kakiyama G, Pandak WM, Sikaroodi M, Gillevet PM. Randomised clinical trial: Lactobacillus GG modulates gut microbiome, metabolome and endotoxemia in patients with cirrhosis. *Aliment Pharmacol Ther* 2014; **39**: 1113-1125 [PMID: 24628464 DOI: 10.1111/apt.12695]

42 **Chiva M**, Soriano G, Rochat I, Peralta C, Rochat F, Llovet T, Mirelis B, Schiffrin EJ, Guarner C, Balanzó J. Effect of Lactobacillus johnsonii La1 and antioxidants on intestinal flora and bacterial translocation in rats with experimental cirrhosis. *J Hepatol* 2002; **37**: 456-462 [PMID: 12217598 DOI: 10.1016/S0168-8278(02)00142-3]

43 **Elzouki AN**. Probiotics and Liver Disease: Where Are We Now and Where Are We Going? *J Clin Gastroenterol* 2016; **50** Suppl 2, Proceedings from the 8th Probiotics, Prebiotics & amp; New Foods for Microbiota and Human Health meeting held in Rome, Italy on September 13-15, 2015: S188-S190 [PMID: 27741172 DOI: 10.1097/MCG.0000000000000712]

44 **Sánchez E**, Nieto JC, Boullosa A, Vidal S, Sancho FJ, Rossi G, Sancho-Bru P, Oms R, Mirelis B, Juárez C, Guarner C, Soriano G. VSL#3 probiotic treatment decreases bacterial translocation in rats with carbon tetrachloride-induced cirrhosis. *Liver Int* 2015; **35**: 735-745 [PMID: 24750552 DOI: 10.1111/liv.12566]

45 **Pawlotsky JM**, Feld JJ, Zeuzem S, Hoofnagle JH. From non-A, non-B hepatitis to hepatitis C virus cure. *J Hepatol* 2015; **62**: S87-S99 [PMID: 25920094 DOI: 10.1016/j.jhep.2015.02.006]

46 **Innes HA**, McDonald SA, Dillon JF, Allen S, Hayes PC, Goldberg D, Mills PR, Barclay ST, Wilks D, Valerio H, Fox R, Bhattacharyya D, Kennedy N, Morris J, Fraser A, Stanley AJ, Bramley P, Hutchinson SJ. Toward a more complete understanding of the association between a hepatitis C sustained viral response and cause-specific outcomes. *Hepatology* 2015; **62**: 355-364 [PMID: 25716707 DOI: 10.1002/hep.27766]

47 **Backus LI**, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2011; **9**: 509-516.e1 [PMID: 21397729 DOI: 10.1016/j.cgh.2011.03.004]

48 **van der Meer AJ**, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584-2593 [PMID: 23268517 DOI: 10.1001/jama.2012.144878]

49 **Bajaj JS**, Sterling RK, Betrapally NS, Nixon DE, Fuchs M, Daita K, Heuman DM, Sikaroodi M, Hylemon PB, White MB, Ganapathy D, Gillevet PM. HCV eradication does not impact gut dysbiosis or systemic inflammation in cirrhotic patients. *Aliment Pharmacol Ther* 2016; **44**: 638-643 [PMID: 27417456 DOI: 10.1111/apt.13732]

P- Reviewer: Chiu KW, d'Arminio Monforte A, Liu J
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com