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EDITORIAL COMMENTARY

# The Gut-Liver Axis in Hepatitis C Virus Infection: A Path Towards Altering the Natural History of Fibrosis Progression?

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**(See the Major Article by Inoue et al on pages 869–77.)**

If a patient is newly diagnosed with chronic hepatitis C virus (HCV) infection, what factors influence the odds that their liver will or has developed significant fibrosis? Will fibrosis impact their health and life expectancy? Do diet and environmental exposures have an impact? What inherited genes are relevant? If HCV is cured, will existing fibrosis regress? Are factors that influence fibrosis progression relevant to fibrosis regression after HCV treatment? How might a patient's provider address these questions?

The World Health Organization estimates that HCV infects 71 million people worldwide and causes nearly 400 000 deaths each year due to complications of liver fibrosis [1]. In addition to the risk of developing hepatocellular carcinoma (HCC), advanced liver fibrosis is associated with high rates of gut bacterial translocation and infection. These include spontaneous bacterial peritonitis, urinary tract infection, and pneumonia that cause substantial morbidity and mortality [2, 3]. In contrast, some patients harbor untreated HCV infection for decades and never develop significant liver fibrosis, with mortality with, rather than from, HCV infection [4]. What accounts for this heterogeneity, and if understood, would this allow for accurate outcome predictions for individuals and rationale design of interventions to alter the natural history of fibrosis progression in those who need it?

Many, but not all, cirrhotic patients cured of chronic HCV infection with interferon-based therapy experience fibrosis regression after cure [5, 6]. This is a heterogeneous response that is also observed in cirrhotic cohorts treated for hepatitis B virus infection [7]. Fortunately, antiviral HCV medications have been developed that can cure all patients who have access to therapy, which results in lower odds of fibrosis progression and HCV-related mortality [6]. Barriers to worldwide HCV eradication and prevention of associated end-stage liver disease are now in the domains of public health, health resource allocation, medication availability, and economics.

Recent detailed genetic and molecular analyses of clinical samples from well-defined clinical cohorts, and from in vitro and animal studies, have advanced our understanding of the mechanisms of fibrosis progression and have helped to address some of the questions outlined above. In addition to the role of diet, environment, and genetics, there is a growing appreciation of the role of the gut-liver axis.

Gut bacteria outnumber cells in the body by 10:1, and some degree of bacterial translocation occurs in healthy patients [8, 9]. Although obligate anaerobic bacteria outnumber aerobic bacteria by 100 or 1000:1, they rarely translocate; rather, gram-negative aerobic bacteria cause most clinically significant infections in advanced liver disease when translocation occurs with increased frequency [3, 10]. The liver is the first stop of venous circulation that harbors translocated bacteria and bacterial products that have traversed the mucosal epithelium and immune system of the gut. Hepatocytes and nonparenchymal cells in the liver, which include Kupffer cells, stellate cells, and other peripheral immune cells, express toll-like receptors (TLRs) that recognize and respond to translocated bacteria and bacterial products, such as TLR4 that recognizes bacterial lipopolysaccharide, and TLR3 and TLR7 that initiate an immune response to viral elements. Hepatic stellate cells, the primary mediators of the fibrogenic cascade and collagen deposition, become activated by inflammation and cell death associated with the recognition and response to bacterial products, resulting in increased fibrogenesis [11]. Thus, the constellation of HCV-induced inflammation, translocation of gut bacteria, and hepatic stellate cell activation would seem adequate to explain why fibrosis occurs during HCV infection.

How then to explain the heterogeneity of fibrosis progression and regression? In humans, single-nucleotide polymorphisms associated with TLR4 correlate with the severity of fibrosis, and in mice,

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genetic inactivation of TLR4 results in suppression of liver fibrosis [11–13]. Furthermore, genetic variability in other genes identified in genome-wide association studies, including interferon lambda genes associated with spontaneous HCV clearance and HCV cure with interferon-based treatment, are associated with fibrosis severity [4, 14, 15]. Thus, host genetics that influence how individuals respond to inflammatory stimuli impact not only HCV virologic outcomes, but also the natural history of fibrosis progression.

So do bacteria that reside in the gut and translocate in health and disease impact fibrosis? From the body of work conducted in murine models of liver disease, it seems clear that the composition of the gut microbiome causatively impacts metabolism, hepatic inflammation through activation of TLRs, and the emergence of HCC and fatty liver disease [2, 16, 17], a relationship being further explored for human disease.

With this background in mind, Inoue et al in this issue of *Clinical Infectious Diseases* present data that contribute to our understanding of the relationships between HCV, liver fibrosis, and the gut microbiome. They examined microbial diversity and composition in a cohort of 166 chronic HCV patients with varying stages of liver disease and 23 healthy controls in a cross-sectional analysis using 16S ribosomal RNA sequencing. They found that patients with advanced liver disease had a reduction in the breadth of gut microbial diversity. Patients with advanced liver fibrosis had decreased relative abundance of *Clostridiales* bacteria, increased *Streptococcus* and *Lactobacillus* bacteria, and higher levels of urease gene expression determined using metagenomics. The authors suggest this could relate to the elevated ammonia and the emergence of encephalopathy seen in patients with decompensated liver disease. Although no cross-sectional study can control for all confounders, the authors assessed the influence of age and proton-pump inhibitor use and report no significant impact on their conclusions.

While the Inoue et al study is the largest study of its kind in HCV, other smaller studies in HCV have reported similar findings [18, 19]. The data are also consistent with studies of patients with advanced liver disease from other etiologies in which a reduction in microbial diversity and composition was associated with the severity of fibrosis [9, 20]. As reduced microbial diversity associated with diet was linked to higher hospitalization risk in patients with advanced liver disease, changes in the microbiome may have direct clinical consequences [21]. Other cross-sectional studies in patients with cirrhosis suggested commensal bacteria of the oral cavity have an increased contribution to the composition of the gut microbiome as liver disease progresses, and the degree of liver fibrosis may have as much or more of an association with the micobiome composition as the causative process causing fibrosis [16, 17, 22]. Intriguingly, a cross-sectional analysis of cirrhotic HCV patients treated with interferon-based therapy revealed no significant microbiome differences based on whether cure was achieved [23]. Longer term studies are needed to determine whether microbiome changes occur over time in patients based on their extent of fibrosis regression and how changes in microbiome diversity affect liver function.

Products that might impact the microbiome are in routine clinical use in patients with advanced liver disease. Although lactulose, a nonabsorbable sugar metabolized by gut flora, and rifaximin, a nonabsorbable antibiotic, impact endotoxemia and hepatic encephalopathy, they were not shown to markedly impact the composition of the gut microbiome; rather, the evidence suggests they may have more of an impact on bacterial function [9, 24–26]. Clinical studies examining modulation of the gut-liver axis will thus need to consider more than microbial composition when considering mechanisms of impact.

Although microbiome changes appear to be associated with advanced liver disease in humans, whether altering the microbiome can impact fibrosis progression and clinical events associated with advanced liver disease remains to be determined. A phase-I trial of the probiotic *Lactobacillus* GG in cirrhotic patients revealed a reduction in endotoxemia, changes in the relative frequency of multiple taxa, and overall reduction in gut dysbiosis [27]; however, this is the only study to our knowledge of this kind [20]. Additional clinical and preclinical studies are needed to understand how the microbiome is modulated by novel therapeutics.

How best then to counsel a patient with chronic HCV infection before or after cure? As is true for many common diseases, the odds of fibrosis progression and regression appear to relate to genetics, environment, and exposures. It is unusual for studies examining fibrosis in cohorts to factor in all of these variables together. Large cohort studies with defined clinical outcomes, availability of biologic materials collected longitudinally, and large data analysis that factors in host genetic, microbiome, demographic, and environmental factors could help further unwind how these factors interrelate to explain heterogeneity in fibrosis progression. Whether or not therapeutics can be developed to modulate the microbiome for clinical benefit remains to be determined. As this work progresses, it remains of paramount importance to remain focused on the intervention best shown to improve liver fibrosis in chronic HCV infection: elimination of the virus itself.

## Notes

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