ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

The Microbiome and the Liver

Bernd Schnabl, MD
Associate Professor
Department of Medicine
University of California, San Diego
La Jolla, California

G&H What is meant by bacterial translocation, and what instigates it?

BS Bacterial translocation is defined as transition of live bacteria or their microbial products from the intestinal lumen to the outside of the intestine: extraintestinal organs, portovenous blood, or systemic circulation. This is facilitated by a leaky gut barrier in which enterocytes are dysfunctional.

Various factors, especially dietary components such as alcohol or a diet rich in fats, contribute to a leaky gut syndrome. Not so long ago, we thought that bacterial translocation was always pathologic, but now we understand that it is actually happening in the normal, healthy body. Our immune system is very strong, and it removes translocated bacteria and bacterial products. Translocation is considered pathologic in the setting of chronic liver disease. In this state, the body is no longer able to remove bacteria and bacterial products, leading to an accumulation of so-called pathogen-associated molecular patterns (PAMPs) in the liver and the systemic circulation.

PAMPs are recognized by toll-like and other pattern recognition receptors. Once the microbial product binds to the receptor, signaling of the innate immune system is initiated. Although this is meant to be the host's immune defense, it can also set off an inflammatory process in the liver, resulting in chronic liver damage and fibrosis.

Pathologic translocation not only leads to progression of liver disease but also to infections in cirrhotic patients. In these cases, translocated live bacteria cause infections in various organs (eg, spontaneous bacterial peritonitis).

G&H What is the relationship between intestinal dysbiosis and liver disease?

BS We have known for a very long time that patients with liver disease due to various etiologies have small intestinal bacterial overgrowth (SIBO). That is, they have a higher bacterial load in their small intestine. In addition, chronic liver disease is associated with qualitative changes in the microbiome. We are learning more about this process thanks to new sequencing techniques. These deep sequencing techniques allow us to identify a large quantity of bacteria, which could otherwise not be identified. Only 15% to 20% of all intestinal bacteria can be cultured using conventional culture techniques. Both quantitative and qualitative changes in the intestinal microflora are defined as dysbiosis. Dysbiosis simply means that there is a disruption of a symbiotic relationship between the host and intestinal bacteria.

There are several factors contributing to dysbiosis, including the host's genetic background, environment, and diet. As for the dietary component, a Western diet that is rich in fat is a major driving factor in changing the gut microbiome and is associated with obesity, nonalcoholic fatty liver disease (NAFLD), and steatohepatitis. In addition, the liver itself can have a profound impact on the composition of the intestinal microbiome. For example, the bile flow from the liver to the intestine is significantly reduced in the setting of cirrhosis and end-stage liver disease. This compromised bile flow contributes to SIBO and dysbiosis.

G&H What have we learned about dysbiosis and liver disease from studies in animal models?

BS My laboratory examined dysbiosis in animal models of various liver diseases, such as toxic liver injury and fibrosis, cholestatic liver disease, alcohol-induced liver disease, and NAFLD. Our results suggest that dietary changes, including a high-fat diet and alcohol consumption, strongly affect the composition of the intestinal microflora, while the absence of bile acids rapidly induces SIBO. We have also shown that alcohol-associated dysbiosis is characterized by a significant reduction in the proportion of probiotic bacteria, such as *Lactococcus, Pediococcus, Lactobacillus,* and *Leuconostoc,* and an increase in the phylum Bacteroidetes. In addition to these qualitative changes, bacterial overgrowth was present throughout the gastrointestinal tract following chronic alcohol feeding.

Dysbiosis might trigger subclinical intestinal inflammation in the lamina propria. Secondary to intestinal inflammation, the intestinal barrier becomes dysfunctional, and translocated bacterial products induce a chronic inflammatory response in the liver. How a dysbiotic microbiome triggers intestinal inflammation is not known and requires further investigation.

Experimental NAFLD has been associated with changes in bacterial metabolites. For example, a dysbiotic microbiome induces choline deficiency in mice fed a high-fat diet. Whether these changes are also causatively linked to liver disease in humans requires future studies.

G&H What preventive measures are taken in at-risk patients to ameliorate dysbiosis indicative of liver pathology?

BS Abstaining from alcohol and reducing caloric intake are beneficial for dysbiosis and alcoholic and nonalcoholic liver disease, respectively.

Hepatic encephalopathy is a common clinical feature of patients with decompensated cirrhosis. There is strong evidence that hepatic encephalopathy is dysbiosis-driven. Intestinal bacteria produce ammonia, which is absorbed mostly in the colon and contributes to neurologic symptoms of patients with decompensated cirrhosis. Standard treatment and secondary prophylaxis target the microbiome. Lactulose or nonabsorbable antibiotics are commonly used.

A dysbiotic microbiota might contribute to translocation of viable bacteria and thereby infections in patients with end-stage liver disease. A small observational study highlighted the clinical importance of intestinal bacterial overgrowth in patients with decompensated cirrhosis. Intestinal decontamination with the nonabsorbable antibiotic rifaximin (Xifaxan, Salix) reduced systemic lipopolysaccharide levels and the severity of liver disease. Obviously, these findings need to be confirmed in larger randomized and placebo-controlled clinical trials.

G&H Is there a role for prebiotics and probiotics in the management of liver fibrosis and cirrhosis?

BS Several trials of probiotics in general liver disease and in cirrhosis specifically have been limited by a lack of stability of the product as a drug, control of diet, or detailed retrieval of the probiotic from stool. A recently published, randomized, placebo-controlled trial of *Lactobacillus rhamnosus* GG in patients with cirrhosis of various etiologies showed that probiotics improve dysbiosis and lower systemic lipopolysaccharide levels. In addition, lactobacilli therapy appears to be safe.

Experimental animal studies showed that prebiotics and probiotics are effective in reducing liver disease. Administration of prebiotics helps the gut to repopulate beneficial bacteria such as bifidobacteria and lactobacilli. *L rhamnosus* GG prevents alcoholic liver disease by stabilizing the gut barrier and reducing bacterial translocation from the intestine to extraintestinal sites.

G&H What is the role of antibiotics in relation to correcting dysbiosis that either leads to or results from liver disease? How should the benefits and risks be weighed?

BS We have been using antibiotics in patients with liver cirrhosis for quite a long time, especially nonabsorbable antibiotics for management of hepatic encephalopathy. In addition, cirrhotic patients with spontaneous bacterial peritonitis will receive oral antibiotics as secondary prophylaxis.

Preclinical studies have demonstrated the benefit of antibiotics in slowing the progression of liver disease. I believe that antibiotics could be used to treat dysbiosis and chronic liver disease; however, there is a risk of emergence of antibiotic-resistant enteric microbes, which might result in bacterial overgrowth and infections of those resistant microbes. A better strategy might be to focus on the host rather than the microbe. For example, the intestinal innate immune system produces antimicrobial molecules that can be considered as endogenous antibiotics. Stimulating the intestinal immune system and the production of antimicrobial molecules might be a good treatment strategy to explore in the future.

G&H What are future clinical research goals in relation to the interplay between the gut microbiome and liver disease?

BS Fecal microbiota transplantation is a relatively new and efficient treatment option for resistant *Clostridium*

difficile infection. It refers to the process of injecting a liquid suspension of stool from a healthy donor into the gastrointestinal tract of a patient to cure a specific disease. Fecal microbiota transplantation is a treatment option that could be explored for patients with liver disease. Because liver disease, in most cases, is a chronic process, fecal microbiota transplantation needs to be a chronic therapy. Rather than undergoing intestinal infusions of donor material on a repeated basis, applications could be developed that package the microbiota or certain bacterial strains into pills that can be given orally over a long period of time. In addition, preclinical research needs to work toward developing better treatments that target the host intestine, the host enterocytes, and also specific intestinal bacteria.

Dr Schnabl has no relevant conflicts of interest to disclose.

Suggested Reading

Bajaj JS, Heuman DM, Hylemon PB, et al. Randomised clinical trial: *Lactobacillus* GG modulates gut microbiome, metabolome and endotoxemia in patients with cirrhosis. *Aliment Pharmacol Ther.* 2014;39(10):1113-1125.

Chen P, Schnabl B. Host-microbiome interactions in alcoholic liver disease. *Gut Liver.* 2014;8(3):237-241.

Kalambokis GN, Tsianos EV. Rifaximin reduces endotoxemia and improves liver function and disease severity in patients with decompensated cirrhosis. *Hepatology.* 2012;55(2):655-656.

Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. *Gastroenterology.* 2014;146(6):1513-1524.

Seki E, Schnabl B. Role of innate immunity and the microbiota in liver fibrosis: crosstalk between the liver and gut. *J Physiol.* 2012;590(pt 3):447-458.