Gut Microbiota and Complications of Liver Disease

Chathur Acharya, MBBS[a], Jasmohan S. Bajaj, MD, MS[b,*]

KEYWORDS

• Cirrhosis • Bile acids • Nonalcoholic steatohepatitis • Alcoholic liver disease
• Dysbiosis • Microbiome • Firmicutes • Bacteroidetes

KEY POINTS

- Intestinal microbial dysbiosis has a large role in the progression of liver disease toward cirrhosis via endotoxemia, intestinal barrier dysfunction, and bile acid changes.
- Decompensation of cirrhosis results in significant changes to the gut microbiome that correlates with complications.
- Dysbiosis predicts decompensation and acute chronic liver failure; hence, every attempt has to be made to modulate this dysbiosis to prevent these outcomes.
- Bile acid changes are an important tool to study microbial function, and the microbiota-modulated bile acid profile plays an important role in progression of human liver disease.

INTRODUCTION

The fundamental understanding of liver disease, especially cirrhosis and its complications, has changed dramatically over the last decade with the introduction of the culture-independent microbiome analysis. Cirrhosis is estimated to affect 0.27% of the general population.[1] Hepatitis C cirrhosis, alcoholic cirrhosis, and nonalcoholic steatohepatitis (NASH)-related cirrhosis are the most common causes, accounting for 53.5%. With the changing demography and increasing obesity, NASH-related cirrhosis is projected to be the most prevalent cause in the future.[2]

There are multiple initial insults spanning from viral hepatitides, fatty liver (alcoholic and nonalcoholic), and biliary stasis to name a few. These initial insults result in

Disclosures: None.
Grant Support: CX10076 VA Merit Review and NIDDK RO1DK089713 (J.S. Bajaj).
[a] Division of General Internal Medicine, Virginia Commonwealth University, 1200 E Broad St, Richmond, VA 23298, USA; [b] Division of Gastroenterology, Hepatology, and Nutrition, McGuire VA Medical Center, Virginia Commonwealth University, 1201 Broad Rock Boulevard, Richmond, VA 23249, USA
* Corresponding author.
E-mail address: jsbajaj@vcu.edu

Gastroenterol Clin N Am 46 (2017) 155–169
http://dx.doi.org/10.1016/j.gtc.2016.09.013
gastro.theclinics.com

inflammation, which is clinically detected by fatigue, malaise, and elevated liver functions. With repeated insult, the inflammation translates to fibrosis, and with continued insults, eventually cirrhosis. Clinically, the precirrhotic state is phenotypically different from the postcirrhotic state with portal hypertension being the major driver of clinical manifestations later. Cirrhosis is associated with complications of hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), variceal bleeding, ascites, and other manifestations of volume overload and also renal complications. However, all cirrhotics do not progress at the same pace, and decompensation is unpredictable. The rate of decompensation for alcoholic cirrhosis is estimated to vary between 4% and 25%[3,4] for NASH cirrhosis, ~2% over 5 years despite minimal histologic progression,[5] and with hepatitis C cirrhosis, the cumulative probability for decompensation at 1 year is ~5%.[6,7] Continuing with the initial insult definitely leads to decompensation, but studies have noted progression of disease from fibrosis to cirrhosis despite cessation of the insulting factor.[8] To understand why certain patients remain stable while others decompensate despite control of inciting insults, investigators have evaluated the gut microbiome and its associated changes in various stages and causes of liver disease to further explain this phenomenon.

The intestinal microbiome itself is a complex composition of microorganisms that is well known to be implicated in cirrhosis and its complications.[9] The metabolic neural pathway also known as the gut-liver–brain axis is a key player in cirrhosis and particularly in HE, and this pathway is strongly regulated by the gut microbiome. Dysbiosis, or an unfavorable change in the composition of the microbiome with a reduction in autochthonous (Firmicutes) bacteria and growth of other taxa (Bacteroidetes, Actinobacteria), is well known to occur in advanced liver disease[10] and other intestinal abnormality.[11,12] Dysbiosis is thought to be central to the proposed pathophysiology of the microbiota and gastrointestinal abnormality for liver disease onset, progression, and development of complication. Typically in dysbiosis there occurs a change in the balance of native Firmicutes to Bacteroidetes species with the former decreasing and the latter increasing. These native bacteria are important for the harmony of the gastrointestinal flora, and as such, for the well-being of the entire body, which is why science now considers the human microbiome as an organ in itself. The autochthonous bacteria produce short-chain fatty acids (SCFAs) that nourish the colonic mucosal cells and reduce local colonic inflammation and also antibacterial peptides and hence help maintain the intestinal barrier.[13] Hence, dysbiosis is associated with increased inflammation and endotoxemia in multiple gastrointestinal abnormality, and in particular, liver disease. The Cirrhosis Dysbiosis Ratio (CDR) is the ratio of autochthonous to nonautochthonous taxa in cirrhosis. The lower the CDR, the more the endotoxemia and more decompensated the cirrhosis.[14]

To give a brief overview of the pathophysiology, the intestine and its barrier, that is, epithelium, Peyers patches, and its lymphoid tissue, act as the first immune system to come into contact with bacteria endotoxins or lipopolysaccharides (LPS), also known as pathogen-associated molecular patterns (PAMPs), that are produced by human microbiota. Because of changes in the intestinal barrier, there is bacterial translocation (BT), which exposes the intestinal immune system to antigens. The intestinal cells have a system of receptors, namely the membranous Toll-like receptors (TLR) and intracellular nucleotide oligomerization domain– like receptors (NLR), that recognize bacterial LPS, bacterial DNA, and peptidoglycans.[15,16] Recognition of the bacterial product by its receptors leads to upregulation of inflammatory mediators like tumor necrosis factor- (TNF-α).[17] Another integral factor in this process is the portal vein that acts as the main conduit for transfer of LPS and other bacterial products from the intestines to the