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Gut Microbiota and Complications of Liver Disease

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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. 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.

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...
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-\((\text{TNF-})\).\(^17\) 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
liver. The final step in this chain is that the metabolites interact with hepatocytes and Kupffer cells via the hepatic TLR and NLR, resulting in changes that promote a cirrhotic morphology.\textsuperscript{18}

In this article, the authors touch upon the proposed pathophysiology of how the microbiome is associated with different liver disease stages and microbiome, focusing mainly on human studies. In \textbf{Tables 1 and 2}, the authors provide details about the main recent clinical studies that show dysbiosis in chronic liver disease (CLD). This review focuses primarily on human nonalcoholic fatty liver disease (NAFLD)/NASH-related liver disease, and alcohol-related liver disease (ALD), because these causes are the paradigms for microbiome-related endotoxemia, dysbiosis, and related changes in the liver. The onset of cirrhosis, regardless of cause, results in changes to the microbiome, which is furthered by decompensation.

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NONALCOHOLIC FATTY LIVER DISEASE

NAFLD and its more sinister evolution, NASH, is slated to be the most common cause for CLD and liver transplantation in the near future. It is estimated that one-third of the general US population has a fatty liver. Up to 20% to 30% of NAFLD patients progress to NASH, and 30% of NASH cases progress to cirrhosis. NAFLD and NASH are commonly associated with the metabolic syndrome, and as noted in previous studies, is a proinflammatory state that is associated with higher levels of serum TNF-α, interleukin-6 (IL-6), and adipokines. The linkages of the gut microbiome and changes with the microbiome with regards to the causation in NAFLD/NASH have been studied for a while now, and the microbiome probably has a larger role in the causation than is known.

Precirrhosis Nonalcoholic Fatty Liver Disease Microbiota Changes

In order to understand why the microbiota is tied into NAFLD and NASH, one needs to first understand how obesity and the metabolic syndrome affect the human microbiome. The human microbiome has been noted to be altered in obesity, and dysbiosis has been well documented. A study by Mouzaki and colleagues looked at 50 patients (of which 22 had NASH) to understand the obesity and dysbiosis paradigm and showed an inverse relationship existed between percentage Bacteriodetes species and the presence of NASH; this confirmed a possible role of dysbiosis in NAFLD. An aspect of dysbiosis in NAFLD that is often overlooked is the effect of the microbiome in extraction of energy from the gut where dysbiosis results in increased production of SCFAs in the intestine with increased monosaccharides, that on transport to the liver activates the proteins that promote hepatic lipogenesis and steatosis. Type 2 diabetes mellitus (DM), an integral component of the metabolic syndrome, has no immediate effect on the microbiome per se, but dysbiosis seems to affect the development of DM. However, once DM sets in, it has a role in dysbiosis and pathogenesis of cirrhosis, as mentioned in a later section.

In humans with NAFLD/NASH, higher levels of LPS in the serum and increased expression of the TNF-α gene in hepatic tissues have been noted, confirming the proinflammatory state associated with these abnormalities. Disruption of the intestinal barrier, that is, disruption of intercellular tight junctions, has been seen in NAFLD and could directly contribute to LPS and other bacterial products reaching the liver. The mechanism underlying disruption of the barrier is thought to be from local colonic inflammation; however, the evidence for this is conflicting and indirect in adult humans, as seen in a study by Pendyala and colleagues, where weight loss in obese individuals resulted in reduced colonic inflammation. Other studies to study colonic inflammation via fecal calprotectin and leptin showed no difference between obese and lean adults. Regardless of the functionality of the intestinal barriers, it has been shown that bacterial LPS are transported out of the intestine to the liver via the portal vein along with chylomicrons that are formed during consumption of high-fat diets. This step is key to aid in the passage of proinflammatory bacterial products past the intestinal barrier, to the liver, where these products interact with their corresponding TLR and induce production of proinflammatory mediators like TNF-α and then subsequent procirrhotic changes. Hence, multiple mechanisms that underlie the development of microbial dysbiosis in NAFLD are seen.

Intestinal Barrier Dysfunction and the Microbiome in Nonalcoholic Fatty Liver Disease

Another prominent factor that could promote endotoxemia in NAFLD and NASH is small intestinal bacterial overgrowth (SIBO). For unclear reasons, the prevalence of
SIBO has been found higher in obesity and NAFLD. The estimated prevalence of SIBO in NAFLD ranges from 50% to 70% from various studies. SIBO has been recognized as an independent risk factor for the severity of hepatic steatosis because of its role in the dysfunction of the intestinal barrier. SIBO in general results in a quantitative change in the microbiome that is associated with dysbiosis, which leads to increased intestinal permeability and increased gut bacterial product translocation, essential in the transition pathway from NAFLD to NASH to cirrhosis. Intestinal microbiota, apart from providing bacterial byproducts, increasing intestinal barrier permeability, also suppress small intestinal secretion of fasting-induced adipocyte factor, which results in increased triglyceride deposition in the hepatocytes. Studies that have looked at the microbiome change in NAFLD have not exactly been able to classify if the changes are SIBO related, and as such, there are no microbiome studies that document the exact changes in NAFLD/NASH from SIBO.

Role of Microbiota and Their Products as a “Second Hit” for Nonalcoholic Steatohepatitis Development

The human microbiome has a strong role in progression of NAFLD to NASH. The 2-hit hypothesis proposed by Day and James puts hepatic steatosis as the first hit. Multiple second hits are possible with this model. Prior papers have studied blood-ethanol concentrations in pediatric NASH subjects and obese non-NASH subjects and noted elevated levels in the former. They deduced that the production of endogenous alcohol by *Escherichia coli* in the intestinal microbiome played a role in NASH development. Another study of 15 adult female patients placed on regulated choline content diets noted that liver fat was inversely proportional to choline deficiency in the diets. Crespo and colleagues studied 52 adult obese patients and looked at the relationship between TNF-α p55 and p75 (TNF-α receptors) and noted overexpression of TNF-α mRNA in NASH patients with increased overexpression with increased severity of NASH. Last, TLR-mediated signaling in Kupffer cells is another proposed second hit. Whatever the second hit, given all the evidence, microbiome has an important role in NAFLD from the pre-cirrhotic to the cirrhotic stages.

Another important mode of evaluating bacterial products is the bile acid (BA) profile. BAs are thought to regulate the microbiome by a potential detergent effect on the cell walls of the intestinal microbacteria and also by interacting with the Farnesoid X receptor (FXR) in the liver, which not only induces excretion of BAs from the liver but also induces antimicrobial peptides production.

The conjugated forms of primary acids BAs (cholic acid [CA] and chenodeoxycholic acid) have been found to be higher in the serum of NAFLD patients, and similarly, the conjugated form of primary and secondary BAs (lithocolic and deoxycholic acid) were noted to be 2.4 times higher in patients with NASH compared with controls. Lake and colleagues studied the composition of BAs in the human livers of NAFLD patients and interestingly found a reduced level of CA and glycodeoxycholic acid and an increase in taurocholic acid and taurodeoxycholic acid. A recent study looking at the fecal composition of NAFLD and NASH adults confirmed a higher fecal BA level with a predominance of primary BAs in the stool of NASH patients (NASH > NAFLD), further clarifying the mechanism by which BAs regulate dysbiosis. To further assess the interplay, Neuschwander-Tetri and colleagues in a multicenter randomized trial studied the effect of obeticholic acid (BA derivative that activates FXR) in NASH patients and noted improvement in the histologic features of NASH based on the NAFLD activity score on liver biopsies.
ALCOHOLIC-RELATED LIVER DISEASE

ALD spans the spectrum of CLD from steatosis, steatohepatitis, liver fibrosis, and eventually cirrhosis, to more acute manifestations like acute alcoholic hepatitis. Along with NAFLD, it is one of the leading causes of CLD. However, only about 10% of chronic alcoholics end up with CLD and only 15% of chronic alcoholics end up developing cirrhosis. Hence, other factors, such as host factors, immunity, and the human microbiome, could contribute to the disease progression.

Precirrhosis Changes to the Microbiome in Alcohol-Related Liver Disease

As with NAFLD/NASH, the microbiome contributes to ALD via intestinal dysbiosis and increased BT. Bode and colleagues first showed a significantly higher number of aerobic and anaerobic bacteria on jejunal aspirates of chronic alcoholics; this held true for alcoholic cirrhotics in a subsequent study. In ALD, endotoxemia has also been noted well before the onset of cirrhosis, supporting the theory of BT. The translocation of PAMPs out of the intestine in ALD would need a faulty intestinal barrier, and Bjarnason and colleagues showed that with chronic alcohol intake there was increased intestinal permeability that persisted up to 2 weeks after cessation of consumption. Studies have shown that even acute alcohol intake (single dose) can lead to increased gastrointestinal permeability. This intestinal permeability has been explained by small bowel injury (duodenal and jejunal), which was noted to occur with ethanol intake, and further studies have shown enlarged intercellular spaces below the tight junctions of the distal duodenal mucosa. In vitro studies have shown that acetaldehyde, a metabolite of ethanol, is responsible for the tight junction disruptions. Acetaldehyde dehydrogenase, which metabolizes acetaldehyde, has a low activity in the colonic mucosa, and theoretically acetaldehyde could persist in the colon and cause local damage. No human or animal studies have been done to this effect yet.

Intestinal Barrier Dysfunction and the Microbiome in Alcohol-Related Liver Disease

As mentioned in the above NALFD section, SIBO is associated with dysbiosis and increased BT, dysmotility, and eventual endotoxemia and is widely prevalent in ALD. Most of the evidence for SIBO changes to the microbiome in ALD is actually from animal model studies. Mutlu and colleagues studied chronic alcoholics with no cirrhosis and in colonic microbiome analysis found dysbiosis with a relative lower median abundance of Bacteroidetes and higher abundance of Proteobacteria. Human studies by Leclercq and colleagues showed that there is increased intestinal permeability in alcoholics, and this was associated with increased abundance of Ruminococcaceae family as well as some bacteria from the Lachnospiraceae family. Interestingly, they also noted that increased intestinal permeability correlated negatively with total number of gut bacteria, but the increased permeability was associated with dysbiosis. As with NAFLD/NASH, with chronic alcoholism, there is a change in the intestinal and serum BA concentration. Kakiyama and colleagues showed that chronic alcoholics had a higher concentration of intestinal secondary BAs and also primary BAs with a higher secondary to primary BA ratio. The same study noted that there was an increase in bacteria from Firmicutes and a reduction in phyla Bacteroidetes in comparison with the non-ALD cirrhosis subjects. Further studies regarding alcoholics and BA variation with the microbiome are needed.

Postcirrhosis Microbiome Changes

Once cirrhosis has set in, the microbiome changes are often due to other mechanisms playing a larger role in promoting dysbiosis. Microbiota changes can have clinically
relevant outcomes such as HE, infections such as SBP, acute-on-chronic liver failure (ACLF), and readmissions.\textsuperscript{14,77,78} In patients with cirrhosis and SBP or HE, lower levels of Firmicutes and higher levels of Bacteroidetes correlated with higher endotoxemia and clinically a higher MELD (model for end-stage liver disease) score correlated with lower levels of autochthonous bacteria. As the liver disease progresses and decompensation ensues, the CDR ratio reduces further and dysbiosis plays a larger role.\textsuperscript{14}

Intestinal barrier dysfunction is noted to be increased in cirrhosis and is also associated with endotoxemia similar to the precirrhotic state.\textsuperscript{79,80} Interestingly, the level of endotoxemia was noted to be higher in alcoholic cirrhosis as compared with other causes in early studies.\textsuperscript{81,82} The microbiome changes after cirrhosis in ALD are similar to that seen in any other cause for cirrhosis, excepting that as cirrhosis onsets the ratio of Bacterioidetes and Firmicutes changes with the former reducing. In most other causes, the opposite happens. Mutlu and colleagues\textsuperscript{74} also showed that among the Bacterioidetes it was the Bacteriodaceae that were reduced in chronic alcoholics, and they had higher levels of Proteobacteria. The CDR similar to SIBO has a direct relationship with the severity of liver disease, and interestingly, alcoholic cirrhosis has been noted to have the lowest CDR.\textsuperscript{14}

In understanding the role of BAs in cirrhosis, Kakiyama and colleagues\textsuperscript{76} showed an increase in BAs in the serum of cirrhotics (NASH related and alcoholic), and that there was a reduced quantity of BAs entering the intestine from the liver as the severity of liver disease progressed. In another study, the same group found that the fecal levels of total BAs were higher in the stool in all alcoholic and nonalcoholic cirrhotics.\textsuperscript{83} Last, DM, irrespective of the metabolic syndrome, has an increased prevalence in cirrhotic patients,\textsuperscript{84} contributes to dysbiosis, and prognosticates complications in cirrhosis.\textsuperscript{85} The presence of DM with insulin use in cirrhosis does alter the gut microbiome, causing a relative increase in Bacteroidetes and other families, but also a reduction in Firmicutes. This change is similar to what is seen in NASH cirrhosis with DM not taking insulin, but does not confer an increased risk for readmissions as seen in a prospective study.\textsuperscript{86}

### Hepatic Encephalopathy

With decompensation of cirrhosis come multiple microbiome changes. While looking at the studies, one must keep in mind that decompensated patients are generally sicker and may also be on microbiome-altering therapy (rifaximin or lactulose). With the onset of HE, there is an increased endotoxemia\textsuperscript{14,87} and the CDR reduces, signaling microbiome changes, although in the study by Bajaj and colleagues,\textsuperscript{88} the predominant change was increased in Bacteroidetes species with no changes in the autochthonous species. Changes to the microbiome have been noted to start with early HE or minimal HE (MHE). Salivary microbiota changes have been shown to correlate with stool microbiota changes and could be explored as a new frontier in immune profiling in cirrhosis. Stool microbiota studies in cirrhotics and MHE noted an increase in Streptococcus salivarius in patients with MHE and an increased blood ammonia level.\textsuperscript{39} In another study, no difference was noted in the stool microbiome between MHE and overt HE (OHE),\textsuperscript{78} although in a similar study by the same group, there was a significant difference in the colonic mucosal microbiome between OHE and healthy subjects with no difference in the MHE and OHE groups.\textsuperscript{77} In more studies, Bajaj and colleagues\textsuperscript{78} showed that certain bacterial taxa such as Proteobacteria correlated with endotoxemia and cognition. Ahluwalia and colleagues\textsuperscript{90} looked at the correlation of intestinal bacteria, HE, and magnetic resonance spectroscopy (MRS) and found that pathogenic taxa (Enterococcaceae, Staphylococcaceae,
Porphyromonadaceae, and Lactobacillaceae) positively correlated with MRS and HE and autohochthonous taxa correlated negatively. Lactulose withdrawal in HE patients did not bring about changes to the microbiome, but in another study, treatment of HE with rifaximin also induces changes to the microbiome with improved endotoxemia and cognition. The changes correlated with changes in serum saturated and unsaturated fatty acids (UFA) with the UFAs increasing and possibly helping in improved brain function. The exact changes to the microbiome taxa by treatment have yet to be documented.

To alter the microbiome to prevent decompensation, prebiotics and probiotics have been studied. In healthy adults, there is no evidence of probiotics resulting in changes; however, in cirrhotics, probiotics belonging to Firmicutes and Actinobacteria phyla have been studied in randomized controlled trials (RCTs) and have been proven to be beneficial. VLS#3 (mixture of multiple probiotic strains) given daily has been proven to reduce the severity of cirrhosis and reduce HE-related admissions in cirrhotics of alcoholic, NASH, and hepatitis C–related causes, although the exact microbiome changes were not noted in this study as well. Lactobacillus GG (LGG) use in an RCT for cirrhotics who were diagnosed to have MHE showed those randomized to LGG reduced dysbiosis through an increased relative abundance of autochthonous taxa and a reduced relative abundance of potentially pathogenic taxa (Enterobacteriaceae and Porphyromonadaceae), along with reduction in endotoxemia.

Spontaneous Bacterial Peritonitis

BT and SIBO are integral to SBP onset in cirrhosis, and hence, dysbiosis plays an important role here. A higher prevalence of gram-negative bacteria of the Enterobacteriaceae family has been noted in cirrhotics with and without decompensation, and it is bacteria from this family that are predominantly noted in SBP ascitic fluid cultures. As seen earlier, with advance in liver disease, the dysbiosis typically worsens. In patients with SBP or infections, the CDR ratio was noted to be lower; there was a higher degree of endotoxemia, and the CDR negatively correlated with endotoxemia. The dysbiosis, however, remained stable for cirrhotics who had not decompensated, indicating that the microbiome changes likely start after decompensation starts.

Prediction of Admissions in Cirrhosis

Bajaj and colleagues studied 278 cirrhotics (all causes), looking at DM as a factor for readmission. In their prospective study with a median readmission time of 90 days, they looked at the stool and sigmoid colon microbiome and noted that cirrhotics that had a nonelective readmission had a reduction in 2 families in the Bacteroidetes phyla. Reduction of Bacteroidetes is associated with increased risk of infection, and hence, on comparing this phyla between alcoholic cirrhotics and NASH cirrhotics given the relative abundance of this phyla in NASH cirrhotics, they have a lesser rate of infection compared with alcoholic cirrhotics.

Acute-on-Chronic-Liver Failure and Death

ACLF is defined as the presence of failure of 2 or more organs in cirrhotic patients. It portends a poor prognosis and has a high mortality. Patients with ACLF have been noted to have a higher level of endotoxemia, and in a large study, patients who developed ACLF and organ failure 30 days after admission could be differentiated from those who did not based on microbiota. This association between ACLF, mortality and microbiota was confirmed by Chen and colleagues, who also noted that...
this dysbiosis is marked in ACLF and can independently predict mortality. Bajaj and colleagues also noted that there was an increase in gram-negative bacteremia on stool microbiome analysis, greater endotoxemia, and these patients had a lower CDR compared with the infected cirrhotics in their study in those who survived. These changes likely occurred well before death and decompensation and may definitively play a role in disease.

**SUMMARY**

To conclude, dysbiosis correlates with endotoxemia, starts early in NAFLD and ALD, and progressively worsens with increasing severity of liver disease. BAs are major proponents of dysbiosis, and alteration in BA profile could profoundly impact liver disease progression. Once cirrhosis sets in, the microbial composition and function alterations worsen and contribute to complications such as HE and ACLF, and can be a predictor of readmissions and mortality.

**REFERENCES**


