Portal blood flows into the liver containing the gut microbiome and its products such as endotoxin and bacterial DNA. The cirrhotic liver acts and detoxifies as the initial site of microbial products. In so-called “leaky gut,” the increased intestinal permeability for bacteria and their products constitutes an important pathogenetic factor for major complications in patients with liver cirrhosis. Prolonged gastric and small intestinal transit may induce intestinal bacterial overgrowth, a condition in which colonic bacteria translocate into the small gut. Cirrhotic patients further show gut dysbiosis characterized by an overgrowth of potentially pathogenic bacteria and a decrease in autochthonous non-pathogenic bacteria. Pathological bacterial translocation (BT) is a contributing factor in the development of various severe complications. Bile acids (BAs) undergo extensive enterohepatic circulation and play important roles in the gut-liver axis. BT-induced inflammation prevents synthesis of BAs in the liver through inhibition of BA-synthesizing enzyme CYP7A1. A lower abundance of 7-α-dehydroxylation gut bacteria leads to decreased conversion of primary to secondary BAs. Decreases in total and secondary BAs may play an important role in the gut dysbiosis characterized by a proinflammatory and toxic gut microbiome inducing BT and endotoxemia, as addressed in my previous reviews. Selective intestinal decontamination by the use of various antimicrobial drugs for management of complications has a long history. Lactobacillus GG decreasing endotoxemia is reported to improve the microbiome with beneficial changes in amino acid, vitamin and secondary BA metabolism. Current approaches for hepatic encephalopathy are the use of nonabsorbable antibiotics and disaccharides. Probiotics may become an additional therapeutic option for advanced liver cirrhosis. (Gut Liver 2021;15:666-676)

Key Words: Gut-liver axis; Endotoxin; Gut dysbiosis; Gut dysmotility; Liver cirrhosis

**INTRODUCTION**

The cirrhotic liver act as the initial site of their detoxification for microbial products from the portal blood. The increased intestinal permeability for bacteria and their products, which is called as leaky gut, is common in liver cirrhosis (LC) and induces an important pathogenetic factor for major complications. Prolonged gut transit induces intestinal bacterial overgrowth, a pathological state in which colonic bacteria translocate into the small intestine. Cirrhotic patients further revealed gut dysbiosis characterized by an overgrowth of potentially pathogenic bacteria and a decrease in autochthonous non-pathogenic bacteria.

Pathological bacterial translocation (BT) is a contributing factor. Bile acids (BAs) undergo extensive enterohepatic circulation. BAs derangement play an important role in the gut dysbiosis characterized by a proinflammatory gut microbiome inducing BT and endotoxemia. Various trial to improve these sequences has been tried for many years. I conducted a PubMed search using search terms including “endotoxin,” “gut liver axis,” and “liver cirrhosis” between 1980 to 2019. This review is fundamentally based on the conference text which I presented in Seoul International Digestive Disease Symposium 2016 (SIDDS) in 2016. Some recent important manuscripts about leaky gut and gut-liver axis in LC ware also included in the present manuscript.
LC is a terminal pathological change in the long history of variable chronic liver diseases characterized by liver fibrosis and the alterations of normal liver architecture into cirrhotic nodules. Subsequent portal hypertension underlies various clinical complications in patients with LC. Bacterial infections explain elevated morbidity and mortality and infections increase mortality four-fold in patients with LC. Although urinary, respiratory, ascitic fluid infections and bacteremia are well-known infections, spontaneous bacterial peritonitis (SBP) frequently developed in advanced cases.

1. Endotoxin and other microbial products which disturb the gut-liver axis

BT or microbial translocation is defined as the migration of viable microorganisms or their products from the gut lumen into the mesenteric lymph nodes and other tissue and organs. Passage of viable bacteria and their products from the intestinal lumen through the intestinal wall and their translocation is the popular backgrounds for the occurrence of infections such as SBP or bacteremia in LC. Bacterial endotoxin (i.e., lipopolysaccharide, LPS) is a component of the Gram-negative bacterial wall and is important as one of pathogen-associated molecular patterns for Toll-like receptors (TLRs). After the translocation microbial products like LPS activate hepatic Kupffer cells (KCs) through pattern recognition receptors, such as TLRs and nucleotide-binding oligomerization domain (NOD)-like receptors. TLRs recognize not only bacterial structural components but also fungal and viral components, which induce innate immune responses through cytokine and chemokine production in the liver. Hepatocytes, KCs, hepatic stellate cells (HSCs) and endothelial cells respond to bacterial products through TLRs and enhance proinflammatory and profibrotic reactions via various cytokines. Early study using limulus amebocyte lysate (LAL) test showed elevated occurrence of systemic endotoxia in patients with LC. The LAL test further detected portal venous endotoxia in 42.9% patients without liver diseases. Quantitative endotoxin assays performed thereafter showed elevated systemic endotoxin values with the progression of LC. Close associations of endotoxia with important complications including hyperdynamic circulation, portal hypertension, renal, pulmonary, cardiac, and coagulation disturbances have been recognized in patients with LC. Recently an indirect assay of endotoxia by endotoxin activity assay (EAA) is prevailing. We noticed high EAA results in cirrhotic patients with refractory ascites, jaundice and hepatic encephalopathy (HE) by this method (Fig. 1). They are positively correlated to serum total bilirubin, fibrin degradation product (FDP) and D-dimer levels and negatively correlated to albumin level and prothrombin time. Selective intestinal decontamination by antibiotics has been reported worldwide.

2. Moderators of the gut liver axis in cirrhotic patients

1) Short chain fatty acids

Human gut microbiota acts substrates such as resistant starch and non-starch polysaccharides not completely hydrolyzed by host enzymes in the small gut. The chief fermentation products are short chain fatty acids (SCFAs) including acetate, propionate, and butyrate. Butyrate provides an energy source for the colonic epithelium. While acetate and propionate work as substrates for gluconeogenesis and lipogenesis, SCFAs exhibit various physiological functions raging from mucoprotection, immune regulation and variable metabolism as well, thus having a direct and indirect effect on human bodies. The main bacteria that produce SCFAs are Escherichia coli and Bacteroides species.

2) Bile acids

BAs are hydroxylated C-24 cyclopentanophenanthrene sterols converted from cholesterol in hepatocytes. Cholesterol 7α-hydroxylase (CYP7A1) synthesizes the dihydroxy BA chenodeoxycholic acid (CDCA) and the trihydroxy BA cholic acid (CA) in the hepatocytes. These primary BAs are conjugated with taurine or glycine before being secreted from the liver and stored in the gallbladder as main and indirect effect on human bodies. The main bacteria that produce SCFAs are Escherichia coli and Bacteroides species. BAs are hydroxylated C-24 cyclopentanophenanthrene sterols converted from cholesterol in hepatocytes. Cholesterol 7α-hydroxylase (CYP7A1) synthesizes the dihydroxy BA chenodeoxycholic acid (CDCA) and the trihydroxy BA cholic acid (CA) in the hepatocytes. These primary BAs are conjugated with taurine or glycine before being secreted from the liver and stored in the gallbladder as main and indirect effect on human bodies. The main bacteria that produce SCFAs are Escherichia coli and Bacteroides species.

Bile acids provide an additional energy source for the colonic epithelium. While acetate and propionate work as substrates for gluconeogenesis and lipogenesis, SCFAs exhibit various physiological functions ranging from mucoprotection, immune regulation and variable metabolism as well, thus having a direct and indirect effect on human bodies. The main bacteria that produce SCFAs are Escherichia coli and Bacteroides species.
biliary components. Eating habit stimulates gallbladder contraction and bile secretion into the small gut. Bile salts can solubilize fats and fat-soluble vitamins and help their uptake. BAs are mostly absorbed in the terminal ileum by the aid of the sodium-dependent BA transporter and flow into the liver through the portal circulation, working as important carrier of portal enterohepatic circulation. The remained BA escapes the enterohepatic circulation and works as substrate for microbial biotransformation in the right colon. Conjugated primary BAs (as CDCA and CA) undergo microbial modifications including deconjugation, dehydroxylation, hydrogenation to synthesize secondary BAs named as lithocholic acid (LCA) and deoxycholic acid (DCA), respectively. The colonic 7α-dehydroxylation bacteria such as Ruminococcaceae, Lachnospiraceae and Blautia mainly work in this conversion process. BAs are now recognized as signaling molecules which activate specific nuclear farnesoid X receptor (FXR) and membrane BA-activated G protein-coupled receptor (GP-BAR1) TGR5 in the intestinal wall. Although CDCA is the most potent endogenous FXR ligand, DCA and LCA, can also activate FXR in a smaller dose. TGR5 is activated by nanomolar concentrations of LCA and micromolar concentrations of CA, DCA, and CDCA. By activating various signaling pathways through the binding to FXR in the enterocytes and the parenchymal hepatocytes and to TGR5 in the non-parenchymal hepatocytes, BAs affect various metabolic processes, including cholesterol, triglyceride and glucose metabolism and inflammatory reactions. BAs also negatively work on gut bacteria through antimicrobial properties and activation of FXR-induced antimicrobial peptide in the small gut. Bile inhibits small intestinal bacterial overgrowth (SIBO) and has a trophic effect on the intestinal mucosa, suppresses epithelial internalization of bacteria, works as detergent actions with anti-adherence effects, deactivates endotoxins and gives powerful effects on immune cells in lymphatic tissue in the intestine. In cirrhotic patients, marked decreases in intestinal intraluminal contents of BAs have been known to increase deconjugation by enteric bacteria. The defect of bile in the intestine facilitates BT and enhances susceptibility to bacterial endotoxins. The transcription factor FXR, a nuclear receptor for conjugated BAs, has now attracted popular attention. Fig. 2 depicts BAs metabolism in the liver and the intestine.

FXR plays a cardinal role in protecting intestinal epithelial integrity and protecting inflammation by depression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling and intestinal stimulating antimicrobial peptide release. The FXR agonist obeticholic acid is regarded to improve intestinal antibacterial defense and suppress permeability as well as to decrease gut BT in experimental LC model. In different cirrhotic models it has considered to decrease portal pressure mediated by depressing intrahepatic vascular resistance. Previous human results using obeticholic acid have revealed promising results to improve histological activity and even reduce fibrosis in different liver disturbance, suppressing the gut-liver axis. BAs are in these ways regarded as a mediator to adjust gut-liver axis.

### GUT DYSFUNCTION, DYSBIOSIS AND LEAKY GUT IN LC

Leaky gut is an essential common word that indicates increased intestinal permeability in various human diseases. Most researchers reported small gut dysmotility in...
cirrhotic patients. Marked changes in the gut contraction pattern were reported in the previous manometric researches. The orocecal transit time (OCTT), particularly in the small intestine, was observed to be prolonged, which was associated with the grade of LC, the development of SIBO and HE in addition to a preceding history of SBP. Bacteriologically, SIBO determined by proximal jejunal aspirates was observed to be present in about 60% of patients with LC and is related to endotoxemia. Delayed small bowel transit was reported in cirrhotic patients accompanied with SIBO, which was related to the abdominal pain and diarrhea. Together with autonomic neuropathy, metabolic derangement including diabetes mellitus, SIBO possibly prolong intestinal transit in patients with LC. Several studies have reported that the gut microbiota is changed in patients with LC especially those with HE (Table 1). A quantitative alteration in Bacteroides/Firmicutes ratio, with an increase in potentially pathogenic bacteria including Enterobacteriaceae together with a reduction in beneficial autochthonous commensals were observed. Bajaj et al. proposed cirrhosis dysbiosis ratio (CDR), which means the ratio of the amounts of beneficial autochthonous taxa including Lachnospiraceae, Ruminococcaceae, Veillonellaceae and Clostridialesuncertain Sedis XIV to those of potentially pathogenic taxa including Enterobacteriaceae and Bacteroidaceae. This CDR was reported to be negatively correlated to the Model for End-Stage Liver Disease score and the blood endotoxin level in advanced LC. A low CDR was noted to predict an early development of organ failure and death. Structural and functional changes in the intestinal mucosa that enhanced intestinal permeability for bacteria and their products, which have been noted in patients with LC. They are chief pathogenetic factors for several grave complications. The etiology of intestinal barrier dysfunction in LC is probably

| Table 1. Changes in Intestinal Microbiota in Liver Cirrhosis |
|-----------------------------------------------|
| **Phylum** | **Class** | **Order** | **Family** | **Genus (species)** |
|-----------------------------------------------|
| Firmicutes † | Bacillales | Bacillales | Staphylococcaceae | Staphylococcus |
| | | | Lactobacillales | Lactobacillus |
| | | | Streptococcaceae | Streptococcus |
| | | | Enterococcaceae | Enterococcus |
| | | | Eubacteriaceae | Eubacterium |
| | | | Ruminococcaceae | Subdoligranulum |
| | | | | Faecalibacterium |
| | | | | Ruminococcus |
| Clostridia | Clostridiales | Clostridiaceae | Clostridium † | Clostridium XI † |
| | | | Eubacteriaceae | Eubacterium |
| | | | Ruminococcaceae | Subdoligranulum |
| | | | | Faecalibacterium |
| | | | | Ruminococcus |
| | | | Lachnospiraceae | Bacterium |
| | | | | Dorea |
| | | | | Blautia |
| Negativicutes † | Selenomonadales | Veillonellaceae † | Butyriviribio (B. crosotus †) |
| | | | Acidaminococcaceae | Veillonella |
| | | | | Acidaminococcus |
| | | | Actinobacteria † | Actinobacteria |
| | | | Bifidobacteriales | Bifidobacteriaceae |
| | | | | Phascolarctobacterium |
| | | | Fusobacteriales | Fusobacteriaceae |
| | | | | Bifidobacterium |
| | | | Bacteroidiales | Prevotellaceae |
| | | | | Bacteroides |
| | | | | Prevotella |
| | | | Rikenellaceae | Paraprevotella (P. xylaniphila) |
| | | | | Alstipes |
| | | | Porphyromonadaceae | Barneamia |
| | | | | Odoribacter |
| | | | | Parabacteroides (P. distasonis) |
| Proteobacteria † | β-Proteobacteria | Burkholderiales | Alcaligenaceae † | Tannerella |
| | | | Burkholderiaceae | |
| | | | Ralstoniaceae | Burkholderia |
| | | | Enterobacteriaceae | Ralstonia |
| | | | | Proteus |
| | | | Pasteurellaceae | Escherichia (E. coli) |
| | | | | |
| | | | | Desulfovibrionales | Desulfovibrio |

Adapted from Fukui H. Diseases 2019;7:58.
multifactorial, including alcohol taking, portal hypertension, SIBO, local infection, endotoxemia, immunological disturbances and continuous medications. The question of whether this intestinal barrier dysfunction estimated by the CDR is accompanied by functional or structural changes in the epithelial tight junction proteins is unresolved. Disruption of the intestinal barrier induces the passage of bacteria and their products from the intestinal lumen, thereby allowing potent inflammatory reactions, such as various infections and affecting portal and systemic circulatory disturbances. Gut dysbiosis, intestinal dysfunction and endotoxemia are key contributors in these processes. All of them induce inflammation in the liver and multiple extrahepatic organs and tissues, enhancing the progression of LC and its complications.

Madrid et al.\textsuperscript{41} studied bowel motility using perfused catheters with external transducers in cirrhotic patients and these affect the migrating motor complex. Absence of cycling activity was often noted in advanced cirrhotic patients with Child-Pugh C grades. In these severe cases, increased amplitudes and frequency of clustered contractions were observed. The authors considered that these findings are probably associated with the prolonged transit time.\textsuperscript{41} Recordings of antroduodenojejunal pressure showed that prolonged clusters were often observed in cirrhotic patients who had portal hypertension.\textsuperscript{41} Combined with the above results from bacterial cultures of jejunal samples, they have speculated that high portal pressure may be associated with the small intestinal dysfunction in cirrhotic patients.\textsuperscript{41}

The OCTT measured by a lactulose load was prolonged in cirrhotic patients with concomitant HE.\textsuperscript{42} The OCTT as determined by a scintigraphic technique was longer in advanced cirrhotic patients who are waiting liver transplantation.\textsuperscript{43} Radiographic procedure showed that 38% of cirrhotic patients had longer small intestinal transit which was associated with abdominal pain and diarrhea.\textsuperscript{44} A later study by means of a wireless motility capsule (Smart-Pill; Medtronic, Minneapolis, MN, USA) by Chander Roland et al.\textsuperscript{45} also showed that decompensated cirrhotic patients have slower intestinal transit times compared with compensated cirrhotic patients. A noninvasive hydrogen breath test revealed that the OCTT was prolonged in cirrhotic patients related to hepatitis B virus infection.\textsuperscript{46} They further reported that patients with hepatocellular carcinoma and viral LC revealed delayed gastrointestinal transit.\textsuperscript{46} Small intestinal dysmotility was more remarkable in cirrhotic patients with a history of SBP.\textsuperscript{47} Another study\textsuperscript{48} showed delayed OCTT in patients with nonalcoholic LC. The primary role of prolonged small intestinal transit in BT of patients with LC can be expected from a pilot trial showing that it precedes the appearance of bacterial DNA in serum and ascites.\textsuperscript{49} Total and left colonic transit times were shorter in cirrhotic patients with accelerated colonic transit is a pathogenetic factor for diarrhea. A magnet-based motility tracking system disclosed that cirrhotic patients with portal hypertension showed faster transit in the proximal small intestine.\textsuperscript{50} Transmucosal passage of microbiota across the intestine is regarded as an important factor for BT.\textsuperscript{51} The gut epithelium plays an important role in immune homeostasis as the first barrier against BT.\textsuperscript{52,53} The gut barrier system of intestinal epithelial cells prevents BT.\textsuperscript{7} The intestinal barrier is constituted mainly by intestinal epithelial cells and their mucinous components.\textsuperscript{5} Intercellular junctions including tight junctions and gap junctions persuade a selective passage of substances.\textsuperscript{5} Structural and functional changes in the intestinal mucosa increasing BT are often observed.\textsuperscript{5} Portal hypertensive gastroduodenopathy defined by enlarged mucosal and submucosal vessels were observed in cirrhotic patients with mild or no inflammatory infiltrate and epithelial erosion.\textsuperscript{54} This condition is related to increased susceptibility to injury from noxious factors reflected in an increased prevalence of peptic ulcer in these cirrhotic patients.\textsuperscript{55} The cause of mucosal damage probably include a decrease in potential differences related to gastric mucosa\textsuperscript{56} and disturbed bicarbonate secretion.\textsuperscript{57,58} Patients with primary biliary cholangitis sometimes revealed increased permeability as well,\textsuperscript{59} although no structural alterations in the intestinal mucosa have been reported. Further debate concerning the intestinal dysfunction in LC were summarized in the previous review.\textsuperscript{6,59} Nonvascular changes such as augmented apoptosis, fibromuscular proliferation, enhanced intraepithelial lymphocytes and shortened and atrophic villi with decreased villous-crypt ratio have been reported in LC.\textsuperscript{60,61} Some of these changes are ascribed to changes in brush border enzymes as well as cell and membrane enzymes.\textsuperscript{62} The capsule endoscopy enabled us to evaluate mucosal alterations in the small intestine with portal hypertensive enteropathy. These changes were inflammation-like abnormalities (edema, granularity, friability and erythema) as well as vascular lesions.\textsuperscript{63} Portal hypertensive enteropathy was noted more than 60% of cirrhotic patients with chronic anemia and a history of variceal bleeding.\textsuperscript{64} The macroscopic change suggesting edema may be mediated by a rise in interstitial hydration due to marked elevation in intestinal capillary filtration in cirrhotic patients with portal hypertension. In case of chronic advanced portal hypertension, the intestinal fluid content was elevated by up to 40%.\textsuperscript{65} Intestinal barrier dysfunction has been regarded as an important pathogenetic factor of several complications in LC.\textsuperscript{66} Portal hypertension, alterations in the intestinal microbiota, inflammation and
oxidative stress can influence the barrier function of both the small and the large intestine and probably result in the occurrence of cirrhotic complications.²⁸,³⁰

There has been a long-lasting discussion about the pathological role of enhanced intestinal permeability in cirrhotic patients.⁶⁷ An Italian study reported that intestinal hyperpermeability was more general in cirrhotic patients with a preceding SBP.²⁸ A Korean study insisted that it was a predictor of bacterial infections.⁶⁹ Three studies reported a higher intestinal permeability in patients with LC and ascites, although other three studies did not report a significant difference.⁶⁹–⁷¹ Contrasting data have been reported on the relationship between HE and intestinal permeability.²⁸ Methodological problems exist when interpreting these conflicting data.⁷²,⁷³ Some authors used sugars,⁶⁸,⁷⁴,⁷⁵ whereas others used more reliable isotope probes.⁶⁸

Mucosal intestinal permeability by urinary excretion of orally taken nonmetabolizable sugars gave the researchers some information about discrimination between paracellular and transcellular fluxes.⁷⁶ The probes seems to traverse the epithelium in one of three ways: paracellular, transcellular aqueous or transcellular lipid.⁷⁷ Villous tight junctions, reflecting the transcellular pathway, are more accessible to intestinal compounds and more selective for smaller compounds compared with crypt tight junctions.⁷⁷ Monosaccharides including mannitol are absorbed through this transcellular pathway and reflect the grade of absorption of small molecules. Disaccharides (i.e., lactulose and mannose) are absorbed through the paracellular junction complex such as tight junctions and extrusion zones of the intervillous spaces reflecting the permeability of larger molecules.⁷⁵,⁷⁸ The urinary ratio of two different probes has been used as an accurate indicator of intestinal permeability, on the bases that the precumosal and postmucosal factors affect the probes equally and the urinary excretion ratio should not be influenced by the above factors.⁷⁷,⁷⁹,⁸⁰ The lactulose/mannitol ratio (LMR) may express an index to evaluate intestinal permeability, and its increase has been regarded as a marker of hyperpermeability.²⁸,³¹ In most studies, this ratio was elevated in patients with LC,²⁸ especially those with advanced LC.⁶⁸,⁷⁵ Alcoholic liver disease also had marked elevations in lactulose excretion with an elevated LMR.³¹ A report from Pascual et al.⁷⁴ described a higher lactulose excretion together with a comparable mannitol excretion in patients with LC. Pijs et al.⁸² noted that small intestinal permeability measured by the lactulose/rhamnose ratio is not changed, whereas large intestinal permeability is increased in patients with compensated LC of mixed etiologies, although they could not deny a tendency of increased small intestinal permeability in alcoholic cirrhosis. As a larger number and increased diversity of microbiome in the large intestine, higher permeability of this site probably elevated risk of BT.⁸³ Parlesak et al. reported that the permeability measured by polyethylene glycol (PEG) disclosing high molecular masses (PEG 1,500 and 4,000) was elevated in cirrhotic patients ascribed to alcoholic drinking. They thought PEG as a reliable probe for the measurement of endotoxin translocation on the bases that its homogenous chemical character, adequately adaptable molecular mass and linear, chain-like figure mimicking endotoxin itself.⁸³ A study by Lee et al.⁸⁴ described that intestinal permeability estimated by PEG 400 and 3,500 was elevated in patients with LC and ascites. In addition, they noted a higher permeability in patients with advanced LC showing Child-Pugh grade class C.⁸⁴ Kim et al.⁸⁵ in Korea wrote that the intestinal permeability index, the percentage of permeability of PEG 3,350 to that of PEG 400, was elevated in cirrhotic patients with gastrointestinal bleeding and infections.

**SMALL INTESTINAL BACTERIAL OVERGROWTH**

SIBO is a pathological state in which colonic bacteria translocate into the small gut attributable to impaired microvillus function, causing a breakdown of intestinal motility and gut homeostasis.⁸⁶,⁸⁷ Gastric acid, intestinal peristalsis, intestinal mucosal immunity and biliopancreatic juice inhibit the occurrence of SIBO in healthy subjects. Abnormalities of these factors can induce SIBO.⁸⁸ SIBO, which means more than 105 total colony-forming units per milliliter of proximal jejunal contents, has been noted to be present in as many as 59% of cirrhotic patients. It is related to endotoxin in the blood.⁸⁹ SIBO was measured by the breath hydrogen test. SIBO diagnosed with this technique is prominent in cirrhotic patients, especially in those with severe liver dysfunction, ascites and associated SBP.⁷⁵ In a study evaluating SIBO using the quantitative cultures of jejunal aspirates, it did not related to the presence of SIBO in patients with LC.⁵ Disturbances in the small bowel manometry and delay in the gut transit is probably associated with the development of SIBO.⁹⁰ The OCTT and small intestinal residence time were prolonged in the patients who had SIBO compared with the patients who had no SIBO.⁹⁰,⁹¹ Enhancement of orocecal transit by taking cisapride is associated with the inhibition of bacterial overgrowth in most patients with LC and bacterial overgrowth.⁵ Prolonged small intestinal transit in cirrhotic patients is expected to enhance the occurrence of SIBO, which may induce abdominal pain and diarrhea.⁶⁶

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The cause of delayed intestinal transit in patients with LC is probably multifactorial. It could be caused by complications of autonomic neuropathy, metabolic derangements including hyperglycemic state. SIBO itself may provoke delayed intestinal transit. Antibiotics can shorten the OCTT, which suggests that bacterial overgrowth per se may induce small gut dysmotility.

The microbiota exerts variable functions including salvaging energy, providing vitamins, inhibiting access for pathogens as well as adjusting immunity. Several studies have showed that the gut microbiota is changed in cirrhotic patients and especially in those who had HE. Culture-independent pyrosequencing of stool enables researchers to recognize decline in microbial diversity and characteristic dysbiosis in LC. A quantitative alteration includes the ratio of Bacteroides/Firmicutes, with an increase in pathogenic bacteria such as Enterobacteriaceae and a reduction of specific commensals (e.g., Lachnospiraceae).

Liu et al. reported that the overgrowth of potentially pathogenic Staphylococcus spp. and Escherichia coli in the intestine of their patients who had viral LC and minimal HE. Another study from China reported that most patient-enriched species were buccal origin, which suggests an invasion of the mouth flora in the stool of cirrhotic patients. Almost half of the enteral bacteria detected in these patients originated from the oropharyngeal regions than those with their absence in healthy subjects. This underlies the concept of deficient intestinal antimicrobial capacity in patients with LC. The above mentioned U.S. study showed that cirrhotic patients with HE had augmented Enterobacteriaceae and Alcaligenaceae compared with control subjects and cirrhotic patients without HE.

Another U.S. study reports the clinical meaning of the mucosa-related flora in cirrhotic patients having HE. The mucosal microbiome was different, with elevated Enterococcus, Veillonella, Megasphaera and Burkholderia and lowered decreased Roseburia abundance in those having HE, although there was no difference in stool microbiota between these cirrhotic patients having HE and those not having HE. The possible method to adjust gut-liver axis in LC is depicted in Fig. 3. Translocated bacteria and their products reach the liver via portal venous blood and affect liver itself and distant organs in patients with LC. Endotoxin is the most described contributor in these processes. All of the bacterial products enhance immune responses causing proinflammatory cytokine and chemokine production in the liver. Nonimmune cells, such as HSCs and sinusoidal endothelial cells, also respond to bacterial products through TLRs.

CONCLUSIONS

Selective intestinal decontamination by the use of various antimicrobial drugs for management of complications has long been tried in patients with LC. Different probiotics has been reported to improve gut dysbiosis and endotoxemia. The trials should be further refined combined with beneficial metabolic changes. Further approaches by antibiotics together with probiotics and prebiotics should be evaluated for the patients with advanced LC, concomitant infection and HE.
CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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