Gut-liver axis in liver cirrhosis: How to manage leaky gut and endotoxemia

Hiroshi Fukui

Hiroshi Fukui, Department of Gastroenterology, Endocrinology and Metabolism, Nara Medical University, Kashihara, Nara 634-8522, Japan
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Correspondence to: Hiroshi Fukui, MD, PhD, Department of Gastroenterology, Endocrinology and Metabolism, Nara Medical University, 840 Shijo-cho Kashihara, Nara 634-8522, Japan. hfukui@naramed-u.ac.jp
Telephone: +81-744-223051
Fax: +81-744-247122
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Abstract
A "leaky gut" may be the cutting edge for the passage of toxins, antigens or bacteria into the body, and may play a pathogenic role in advanced liver cirrhosis and its complications. Plasma endotoxin levels have been admitted as a surrogate marker of bacterial translocation and close relations of endotoxia to hyperdynamic circulation, portal hypertension, renal, cardiac, pulmonary and coagulation disturbances have been reported. Bacterial overgrowth, increased intestinal permeability, failure to inactivate endotoxin, activated innate immunity are all likely to play a role in the pathological states of bacterial translocation. Therapeutic approach by management of the gut-liver axis by antibiotics, probiotics, symbiotics, prebiotics and their combinations may improve the clinical course of cirrhotic patients. Special concern should be paid on anti-endotoxin treatment. Adequate management of the gut-liver axis may be effective for prevention of liver cirrhosis itself by inhibiting the progression of fibrosis.

Key words: Gut-liver axis; Liver cirrhosis; Pathogenesis; Complications; Endotoxia; Bacterial translocation; Leaky gut; Toll-like receptors; Selective intestinal decontamination; Probiotics

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Core tip: A "leaky gut" may be the cutting edge for the passage of toxins, antigens or bacteria into the body, and may play a pathogenic role in advanced liver cirrhosis and its complications. More attention should be paid to the role of intestinal bacteria and bacterial products in the field of Hepatology. Here, I would like to overview the history of endotoxin assay in the blood, clinical significance of endotoxia in liver cirrhosis and then shift to the topic of gut and liver in general. Understanding of the gut-liver axis, leaky gut and endotoxia in cirrhosis may give us new ideas.

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INTRODUCTION
Bacterial infections account for significant morbidity
and mortality in patients with liver cirrhosis. Infections increase mortality 4-fold in cirrhotic patients. Although urinary, respiratory, ascitic fluid infections and bacteremia are common infectious complications, spontaneous bacterial peritonitis (SBP) occurs most frequently. A vast majority of such infections are due to enteric gram-negative bacteria, mainly Enterobacteriaceae. Passage of viable bacteria from the intestinal lumen through the intestinal wall and to mesenteric lymph nodes (MLNs) and other sites, defined as bacterial translocation (BT), explains the development of SBP. The concept of BT was later broadened to microbial products or their fragments, such as endotoxin (lipopolysaccharide (LPS)), peptidoglycan, lipopeptides and bacterial DNA. The liver receives portal blood containing these microbial products and acts as the initial site of their filtration and detoxication. These defense mechanisms are impaired in the cirrhotic liver, which finally results in spillover of these products and secretion of various inflammatory mediators.

LPS is a major component of the gram-negative bacterial wall. Its detection in the blood has a long history and is still not complete with several methodological difficulties. However, the endotoxemia detected by the Limulus-lysate test or its modifications has been well correlated to the severity, complications and mortality of liver cirrhosis. Control of endotoxemia is still considered to be the mainstay of therapy for advanced liver cirrhosis.

Here, I would like to overview the history of endotoxin assay in the blood, clinical significance of endotoxemia in liver cirrhosis and then shift to the topic of gut and liver in general. Understanding of the gut-liver axis, leaky gut and endotoxemia in cirrhosis may give us new ideas for hepatology tomorrow.

DETECTION OF ENDOTOXEMIA IN PATIENTS WITH LIVER CIRRHOSIS

Levels of bacterial LPS are increased in the portal and/or systemic circulation in liver cirrhosis. Endotoxemia was first demonstrated by the Limulus amebocyte lysate (LAL) test and later by several quantitative assay, such as the chromogenic Limulus assay and the turbidimetric endotoxin assay. Although endotoxemia is now considered to be a common feature of liver cirrhosis, there has been much debate and still disagreement about plasma endotoxin levels.

Early study using LAL test revealed that systemic endotoxemia in liver cirrhosis occurred with a frequency of 15 of 31 compared with 2 of 21 venous samples and 9 of 21 portal venous samples from patients without liver disease. Tarao et al. reported that death occurred within 6 mo in 47.8% of the patients with a positive endotoxin test, whereas only 16.7% of those with a negative test died in the same period. Clemente et al. showed that a positive LAL test was almost exclusively associated with a progressive functional renal failure (8 of 10 patients) and all but one of them died. Endotoxemia was also associated with hemorrhage due to acute erosions of the gastric mucosa (6 of 7 patients). On the contrary, Gaeta et al. found no significant difference in the frequency of endotoxia between patients with impaired and unimpaired renal blood flow. Moreover, no relation was found between endotoxin plasma levels and renal blood flow in their study. Bode et al. reported that the prevalence of endotoxia was not significantly higher in cirrhotics with ascites or esophageal varices when compared to the subgroup without ascites or esophageal varices. They additionally found endotoxia more frequently in patients with alcoholic cirrhosis (67.3%) than in patients with non-alcoholic cirrhosis (45.5%).

In general, nonspecific gelation has been reported by this LAL test, and interpretation of the results has often caused confusion. Finally, Fulenwider et al. reported that they could not detect any endotoxin by the LAL test in peripheral plasma, portal plasma and ascites. They concluded that the ubiquity of endotoxin, with the attendant opportunities for specimen contamination, is the most likely explanation for the high prevalence of endotoxin in the plasma and ascites of cirrhotic patients.

In 1978, Iwanaga et al. developed a quantitative endotoxin assay using a synthetic chromogenic peptide as a substrate for the endotoxin-sensitive Limulus enzyme. This assay has been shown to give reliable results for minute amount of endotoxin in water. However, measurements of endotoxin in blood present some difficulties. Major problems in plasma endotoxin assay are (1) disagreement about the best way of preparing standard curves; (2) lack of an optimal method for eliminating plasma inhibitors for endotoxin assay; and (3) necessity of endotoxin-specific chromogenic substrate. We have insisted that a standard curve should be prepared for each individual plasma sample in the endotoxin determination, because ideal 100% recovery of endotoxin could not be validated in any trial of plasma pretreatment. The internal standard is especially necessary in the perchloric acid treatment, where strict adjustment of pH in samples is difficult before the chromogenic assay. Our study demonstrated hidden extra portion of endotoxin in plasma of patients with chronic liver diseases, using new way of plasma pretreatment either by Tween 80 in the dilution and heating method or by triethylamine in the perchloric acid method. The chromogenic substrate widely used in the world is considered to react not only endotoxin but also other substances such as (1,3)-β-D-glucan, component of cell wall of fungus. Endotoxin-specific chromogenic substrate was produced by removing G-factor from the lysate.

Although most studies on plasma endotoxin
levels ignored these points, using simply the dilution and heating method and non-specific chromogenic substrate, results obtained were generally useful for evaluation of the clinical significance in liver cirrhosis. Lumsden et al.\(^{22}\) found that endotoxin levels in the portal venous blood was significantly higher than that in the peripheral venous blood, although there was a wide variability. However, neither hepatic nor peripheral venous endotoxin levels correlated significantly with a variety of clinical, biochemical or radiological parameters\(^{22}\). Tachiyama et al.\(^{23}\) also confirmed that endotoxin levels in the portal blood was higher than that in the peripheral venous blood by their Limulus gelation turbidimetric LAL assay. Moreover, they found that portal endotoxin levels in patients with cirrhosis was higher than those without cirrhosis\(^{23}\). This finding suggests an enhanced intestinal production and/or absorption of endotoxin in liver cirrhosis, which later developed the discussion on bacterial overgrowth and leaky gut in liver cirrhosis. Bigatello et al.\(^{24}\) detected endotoxemia in 36 of 39 cirrhotic patients and in none of healthy volunteers by their chromogenic LAL test. They found that systemic endotoxia was higher in patients with hepatic encephalopathy after esophageal variceal hemorrhage than in well-compensated cirrhotics. It was higher in patients with deep coma than in those with light coma and also higher in those who died than in those who survived. They concluded endotoxia without sepsis is a common finding in cirrhosis and increasing levels of endotoxia are associated with hepatic failure, encephalopathy, and death\(^{24}\).

We found higher plasma endotoxin level in patients with alcoholic cirrhosis than in patients with non-alcoholic cirrhosis with an improved chromogenic substrate assay, using individual standard curves for each plasma sample\(^{25}\). On admission endotoxin concentrations in alcoholics with fatty liver were similarly elevated as observed in alcoholic cirrhosis. In 6 out of 12 patients with fatty liver or alcoholic hepatitis, in whom a second sample of plasma was investigated after 6 to 8 d, endotoxemia was no longer detectable. The results indicate that, irrespective of the stage of liver disease, alcohol abuse favors the development of endotoxia\(^{25}\). In the measurement of plasma endotoxin by the dilution and heating method, we frequently experienced that plasma endotoxin level in patients with advanced liver cirrhosis was unexpectedly low and speculated that some part of plasma endotoxin might be lost in the procedure of dilution and heating. To overcome this situation, we added a detergent Tween 80 after heating plasma and discovered much hidden endotoxin in the sample\(^{26}\). Significantly higher plasma endotoxin levels in cirrhotics with upper gastrointestinal (GI) bleeding compared with those without upper GI bleeding was detected by this Tween 80 method\(^{26}\).

To attain endotoxin-specific chromogenic assay, we further improved our method using triethylamine in the perchloric acid method and endotoxin-specific substrate Endospecy (Seikagaku Kogyo Co., Tokyo, Japan) with kinetic analysis\(^{19,20}\). A final pH of the assay sample was always adjusted to 7 by careful titration of triethylamine\(^{19}\). The results of our measurement of plasma endotoxin in 90 patients with liver cirrhosis and 11 patients with chronic hepatitis with this method were summarized as follows: (1) there was an increase of plasma endotoxin with the progression of chronic liver disease; (2) in patients with bleeding from esophageal varices, plasma endotoxin increased for 3 d after the bleeding and thereafter decreased; and (3) endotoxin level increased as the progression of Child-Pugh grades and was negatively related to prothrombin time\(^{18}\).

**RELATIONSHIP OF ENDOTOXEMIA TO PATHOGENESIS OF CIRRHOSIS AND ITS COMPLICATIONS**

**Hyperdynamic circulation**

Hyperdynamic circulation characterized by hypotension, low systemic vascular resistance, high cardiac output and a reduced sensitivity to vasoconstrictors are features of cirrhosis. These cardiovascular changes might be the result of increased synthesis of a vasodilator\(^{27}\). Nitric oxide derived from vascular endothelium is a potent vasodilator that plays a key role in the homeostasis of blood pressure\(^{28}\). Cirrhotic patients showed significant increases in serum nitrate/nitrate which was significantly correlated with endotoxia\(^{29}\). Oral administration of colistin to 15 cirrhotic patients reduced significantly plasma endotoxin levels and serum nitrate/nitrate levels\(^{30}\). A lower systemic vascular resistance and a higher cardiac output were found in cirrhotics with endotoxemia than in those without endotoxia\(^{29}\). These studies support that endotoxia may be responsible, at least in part, for the hyperdynamic circulation found in patients with liver cirrhosis. On the contrary, Campillo et al.\(^{30}\) showed that serum nitrate levels did not correlate with endotoxia and that cardiac index did not correlate with serum nitrate levels, urine nitrate excretion and endotoxia. Plasma interleukin (IL)-6 levels were correlated negatively with systemic vascular resistance in patients with cirrhosis, but no correlation was observed between plasma endotoxin levels and plasma IL-6 levels\(^{31}\). Finally, Bhimani et al.\(^{32}\) concluded from their experiments that an endotoxin-induced increase in mesenteric iNOS activity and a decrease in hepatic cNOS activity may account for, respectively, the hyperdynamic visceral circulation and the increased intrahepatic resistance of cirrhosis. Although the role of endotoxin on the hyperdynamic circulation still remains controversial, endotoxia, possibly from gut-derived bacterial translocation, causes induction of
nitric oxide (NO) synthase (NOS) leading to increased vascular NO production, which is the primary stimulus for the development of vasodilation in cirrhosis and its accompanying clinical manifestations\cite{33}.

**Portal hypertension**

In cirrhosis, portal hypertension can promote bacterial translocation and increase serum endotoxin levels. Vice versa, endotoxin aggravates portal hypertension by induction of systemic and splanchic vasodilation, and by triggering hepatic inflammatory response via tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\))\cite{34}. Endotoxin levels correlated with hemodynamic derangement in cirrhotic severe portal hypertension, and with levels of soluble TNF-\(\alpha\) receptors in patients with alcoholic liver cirrhosis receiving elective transjugular intrahepatic portosystemic shunt\cite{34}. Thromboxane (TX) A\(2\) has been suggested to play a significant role in the development of portal hypertension in fibrosis, and Kupffer cell (KC) derived TXA\(2\) has been shown to mediate the hyperresponsiveness of the portal circulation to the vasocostrictive actions of endothelin-1 during endotoxemia\cite{35}. The double stresses of early fibrosis additively activate KC and release increased amount of TXA\(2\) in response to ET-1, which leads to the increased portal resistance and ultimately hepatic microcirculatory dysfunction\cite{35}. Steib et al\cite{36} concluded from their experiment in bile-duct ligated rats that upregulation of Toll-like receptors (TLR)4 and MyD88 expression in fibrotic livers confers hypersensitivity to LPS. This may lead to escalation of portal hypertension by production of TX and Cys-leucotriene after LPS-induced KC activation.

**Hepatic encephalopathy**

Except for the early human study by Bigatello et al\cite{24}, the role of endotoxin on hepatic encephalopathy had not been investigated until recently. Wright et al\cite{37} showed that the injection of endotoxin into cirrhotic rats induced pre-coma and exacerbates cytotoxic edema because of the synergistic effect of hyperammonemia and the induced inflammatory response. Bajaj et al\cite{38} further extended the problem to microbiome in the intestine and concluded that cirrhosis with hepatic encephalopathy is associated with significant alterations in the stool microbiome compared with healthy individuals. Specific bacterial families (Alcaligenaceae, Porphyromonadaceae, Enterobacteriaceae) are strongly associated with cognition and inflammation in hepatic encephalopathy. The central role of ammonia in the pathogenesis of hepatic encephalopathy is incontrovertible. However, there is a robust evidence indicating the importance of inflammation in exacerbating the neurological effects of hepatic encephalopathy\cite{39}. Sterile inflammation by circulating endotoxin from the gut (bacterial translocation) inducing immune dysfunction may have some effect via the release of pro-inflammatory mediators which directly signal to the brain\cite{39}.

**Renal disturbance**

Endotoxin is a well-known renal vasoconstrictor. Deleterious effect of endotoxin on kidney has been confirmed in various animals, i.e., dogs\cite{40}, mouse\cite{41} and bile-duct ligated rats\cite{42}. Uchihara et al\cite{43} found that plasma endothelin levels were significantly higher in patients with endotoxemia than in those without and were negatively correlated to creatinine clearance in cirrhics. They concluded that plasma endothelin closely related to endotoxemia, may play a contributory role in kidney dysfunction in patients with cirrhosis\cite{43}.

As stated above, there has been a disagreement about the relation of endotoxemia to renal disturbance in cirrhosis. Close correlation reported in the early period using LAL test\cite{7,44,45} was not always validated in the later period using quantitative LAL test\cite{30}. However, experimental evidences together with beneficial effect of non-absorbable antibiotics support the pathogenetic roles of endotoxin in the renal disturbance.

Shah et al\cite{44} demonstrated in their bile-duct ligated rats that kidneys in cirrhosis show an increased expression of TLR4, NF\(\kappa\)B, and the pro-inflammatory cytokine TNF-\(\alpha\), which makes them susceptible to a further inflammatory insult. This increased susceptibility to LPS can be prevented with selective decontamination by norfloxacin\cite{46}. The effect of selective decontamination for renal disturbance to patients with liver cirrhosis was first reported with paromomycin sulfate\cite{47} and recently by rifaximin\cite{48}.

SBP is the most dangerous infectious complication arising in patients with cirrhosis and ascites. It is associated with high serum and ascitic fluid levels of proinflammatory cytokines. These patients are predisposed to the development of renal impairment, type 1 hepatorenal syndrome\cite{49}. Albumin infusion improves renal function in acutely decompensated cirrhotic patients with acute kidney injury by impacting on renal blood flow autoregulation. This is possibly achieved through endothelial stabilization and a reduction in the sympathetic tone, endotoxemia and oxidative stress\cite{50}.

**Cirrhotic cardiomyopathy**

Liver cirrhosis is associated with several cardiovascular abnormalities. Despite an increased baseline cardiac output, cirrhotic patients have a suboptimal ventricular response to stress. This phenomenon is called cirrhotic cardiomyopathy. The pathogenesis of this syndrome is multifactorial and includes diminished \(\beta\)-adrenergic receptor signal transduction, cardiomyocyte cellular plasma membrane dysfunction, and increased activity or levels of cardiodepressant substances such as cytokines, endogenous cannabinoids, and nitric oxide\cite{51}. Patients with severe cirrhotic cardiomyopathy have higher lipopolysaccharide binding protein (LBP) levels, which are significantly correlated with the degree of diastolic dysfunction. This findings support a potential role of bacterial endotoxemia on the aggravation of cardiomyopathy in cirrhotic patients\cite{52}.
The development of severe renal failure type 1 HRS seems to be related to a cardiac systolic dysfunction[33]. In addition to the above myocardial dysfunction, the release of endotoxins and biologically active substances such as inflammatory cytokines, nitric oxide, carbon monoxide related to bacterial infection may further impair cardiac function in patients with advanced cirrhosis[34].

Hepatopulmonary syndrome
Hepatopulmonary syndrome (HPS) is an important cause of dyspnea and hypoxia in 10%-30% of patients with cirrhosis[35]. It is due to vasodilation and angiogenesis in the pulmonary vascular bed, which leads to ventilation-perfusion mismatching, diffusion limitation to oxygen exchange, and arteriovenous shunting[35].

In experimental studies, Zhang et al[56] demonstrated that progression and severity of HPS as indicated by both increased pulmonary capillaries and histological changes are closely associated with endotoxin levels in the cirrhotic rat model. They thought that overproduction of TNF-α due to endotoxin stimulation of KCs via mitogen-activated protein kinase signal transduction pathway may be a major mechanism mediating the pathologic alterations of HPS[57]. There was a case report[58] that showed a beneficial effect of oral norfloxacin for hypoxia in a patient with this syndrome. The authors speculated that norfloxacin reduced endotoxemia and concomitant nitric oxide production in patients with cirrhosis. However, a following pilot study of intestinal decontamination with norfloxacin in patients with HPS, in an attempt to reduce endotoxia, failed to produce any improvement in gas exchange[59].

Coagulation and platelet abnormalities
Patients with advanced liver cirrhosis paradoxically have both risks of bleeding and thrombosis. They should face fragile balance between hypercoagulability and hypocoagulability related to reduced synthesis of clotting factors, accelerated fibrinolysis, platelet dysfunction and low-grade intravascular coagulation. Hyperfibrinolysis is not a primary phenomenon but occurs as a consequence of clotting activation and that endotoxemia might play a pathophysiological role[95]. Cirrhotic patients are at increased risk for thrombotic events, particularly in the portal venous system[60]. In cirrhotics, plasma levels of von Willebrand factor (vWF) antigen and endotoxemia progressively increased from Child Pugh’s classification A to class C[61]. vWF is a marker of endothelial perturbation and endotoxin releases vWF from endothelial cells in vitro[61]. Endothelial procoagulant activation induced by low-grade endotoxemia may represent a trigger for systemic clotting activation in liver cirrhosis patients[62]. Violi et al[63] reported that endotoxemia was directly correlated with F1 + 2[59] and D-dimer. These studies show that an ongoing prothrombotic state is present in the portal circulation of cirrhotic patients and may play a pivotal role in the thrombotic episodes[63]. They further confirmed that monocyte expression of tissue factor (TF) was significantly correlated with plasma levels of F1 + 2 and with endotoxemia[64]. TF mRNA expression was detected only in three patients with endotoxemia[64].

Decreased plasma ADAMTS13 activity results in the accumulation of unusually large vWF multimer (UL-VWF) and the formation of platelet thrombi[65]. Uemura et al[65] showed that ADAMTS13 activity decreased with increasing severity of liver disease (controls means 100%, chronic hepatitis 87%, Child A cirrhosis 79%, Child B cirrhosis 63%, and Child C cirrhosis 31%), and showed severe deficiency (< 3% of controls) in five end-stage cirrhotics. This ADAMTS13 activity may be a useful prognostic marker that is equal or superior to the Child-Turcotte-Pugh score and the Model for End-Stage Liver Disease score to predict not only the short-term prognosis but also the long-term survival of the cirrhotic patients[66]. As we found that endotoxemia was inversely correlated with ADAMTS13 activity and was higher in patients with UL-VWF than those without in patients with alcoholic hepatitis[67], this relation should be estimated in liver cirrhosis.

GUT-LIVER AXIS IN HEALTH AND LIVER CIRRHOSIS
The gut and the liver are the key organs in nutrient absorption and metabolism. Bile acids, drugs, and toxins undergo extensive enterohepatic circulation. Bile acids play a major role in several hepatic and intestinal diseases. Endotoxins deriving from intestinal Gram-negative bacteria are important in the pathogenesis of liver and systemic diseases[68]. Gut flora and bacterial translocation play important roles in the pathogenesis of chronic liver disease, including cirrhosis and its complications[69]. Intestinal bacterial overgrowth and increased bacterial translocation of gut flora from the intestinal lumen predispose patients to bacterial infections and major complications[69].

Bacterial translocation
BT or microbial translocation is defined as the migration of viable microorganisms or bacterial products (i.e., bacterial LPS, peptidoglycan, and lipopeptides) from the intestinal lumen to the mesenteric lymph nodes and other extraintestinal sites[70]. Passage of viable bacteria from the intestinal lumen through the intestinal wall and its translocation to mesenteric lymph nodes and other sites is the accepted pathogenic mechanism for the development of spontaneous infections, such as SBP or bacteremia[4]. Bacterial products, such as endotoxin, or bacterial DNA can translocate to extra-intestinal sites.
and promote an immunological response similar to that produced by viable bacteria. Pathological BT is a contributing factor in the development of complications in cirrhosis, not only in infections, but by exerting a profound inflammatory state and exacerbating the hemodynamic derangement \(^4,71\).

**Small intestinal bacterial overgrowth**

Small intestinal bacterial overgrowth (SIBO), defined as \(\geq 10^5\) total colony-forming units per milliliter of proximal jejunal aspirates, was present in 59% of cirrhotic patients and is associated with systemic endotoxemia \(^72\). SIBO related with a slowed intestinal transit, low acid gastric secretion, intestinal immunological factors and pancreatic and biliary secretions, is important factor promoting BT \(^61\). Cirrhotic rats with intestinal bacterial overgrowth had a significantly higher rate of translocation and slower intestinal transit than those without it \(^73\).

SIBO, determined by the breath hydrogen test, is common in patients with cirrhosis, especially in those with advanced liver dysfunction and in those with a history of SBP \(^4,74,75\). In a study that estimated SIBO by more reliable quantitative cultures of jejunal aspirates, the occurrence of SBP did not correlate with the presence of SIBO \(^4\). Sánchez et al \(^76\) reported that the increase of intestinal aerobic bacteria in experimental cirrhosis is associated with translocation and is supposed to play an important role in the development of BT. Impaired motility may be implicated in the pathogenesis of intestinal bacterial overgrowth \(^76\). Gut flora imbalances, higher levels of *Enterobacteriaceae* result in significant changes in BT and liver function in cirrhotic rats \(^77\).

Dietary habits, by increasing the percentage of intestinal Gram-negative endotoxin producers, may accelerate liver fibrogenesis, introducing dysbiosis as a cofactor contributing to chronic liver injury in nonalcoholic fatty liver disease \(^78\). Liver cirrhosis disturbs intestinal microbiota and innate immunity-related genes, which contributes to endotoxemia and bacterial translocation. These had not completely recovered in cirrhotic rats until 1 mo after orthotopic liver transplantation \(^79\).

**Increased intestinal permeability**

The gut epithelium plays an important role in the immune homeostasis in the gut as the first barrier against the bacterial translocation \(^80,81\). Because gut barrier system by intestinal epithelial cells prevent translocation of large amounts of bacteria and bacterial products, very small amount of them can reach the liver in a healthy state \(^82\). The intestinal barrier is formed mainly by intestinal epithelial cells and their mucinous components \(^4\). In addition, intercellular junctions such as tight junctions and gap junctions allow selective passage of substances \(^4\). Structural and functional changes in the intestinal mucosa that increase intestinal permeability of bacteria and its products have been found in patients with liver cirrhosis \(^83\). This intestinal barrier dysfunction may be an important pathogenetic factor for several complications of liver cirrhosis \(^83\). Characteristics of cirrhosis itself, including portal hypertension, alterations in the intestinal microbiota, inflammation and oxidative stress can affect barrier function of both small and large intestine and may contribute to the development of complications \(^71\). Although gut barrier function did not show a significant relationship with endotoxemia, increased intestinal permeability may be a significant finding that at least in part is associated with the pathophysiology of viral liver cirrhosis \(^84\).

There is a long-standing debate about the presence and role of increased intestinal permeability in patients with cirrhosis \(^85\). Some authors have shown an association between increased intestinal permeability and severity of liver cirrhosis assessed by the Child-Pugh classification \(^85-87\), but others have failed to reproduce these results \(^86-90\). Methodological problems should be taken into account when interpreting these conflicting results \(^91\). Some authors used sugars \(^86,87,92\) and others used isotope probes \(^85,88-90\), the latter considered to be the gold standard as the probes are not synthesized or digested in the human body \(^85\). However, the assessment of the mucosal intestinal permeability by urinary excretion of orally administered non-metabolizable sugars gave us some information on the discrimination between transcellular and paracellular fluxes \(^93\).

Monosaccharides, such as mannitol, are absorbed through the transcellular pathway and reflect the extent of absorption of small molecules. Disaccharides, such as lactulose, are absorbed through the paracellular junction complex (the tight junctions) and extrusion zones of the inter villous spaces, which corresponds to the permeability of larger molecules \(^92,94\). Mannitol absorption as assessed by urinary excretion can be considered as an indicator of the mucosal absorptive area, and lactulose absorption as a measure of the integrity of intestinal mucosal tight junctions \(^94,95\).

The lactulose/mannitol (L/M) ratio (LMR) thus comprises an index to appraise intestinal permeability and its increase has been traditionally used as a marker of hyperpermeability \(^96\). This ratio has been reported to be elevated in patients with liver cirrhosis \(^92\) and to be markedly elevated in advanced stage \(^86,87\). This increase in intestinal permeability determined by LMR has been reported in several previous studies \(^96,97\). Alcoholics with liver disease also had marked and statistically significant increases in lactulose excretion in addition to increased LMR \(^96\).

The abnormally elevated LMR in alcoholics with liver disease is not simply due to decreased mannitol excretion but represents increased gut permeability \(^96\). Pascual et al \(^97\) found a significantly higher lactulose excretion (\(\%_L\)) with a comparable mannitol excretion.
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reduced bacterial content to normal levels and improves bacterial translocation and endotoxemia in cirrhotic rats. Further studies should evaluate the potential benefits of bile acids in humans.

**Toll-like receptors and liver disease**

Translocated microbial products activate KCs in the liver through pattern recognition receptors, such as toll-like receptors (TLRs) and NOD-like receptors. TLRs, recognize pathogen-derived molecules, i.e., structural components unique to bacteria, fungi, and virus- and activate innate immune responses including cytokine production in the liver. It should be noted that hepatic non-immune cells, such as hepatic stellate cells (HSCs) and endothelial cells, also respond to bacterial products through TLRs.

Recently, more than 10 members of the TLR family have been identified. TLR4 was the first identified isoform that responds primarily to LPS. LPS binds to TLR4 with co-receptor CD14 and MD-2. TLR2 heterodimerizes with TLR1 or TLR6 to recognize lipoprotein and peptidoglycan derived from Gram-positive bacteria. Bacterial flagellin is recognized by TLR5. Intracellular TLR3 and TLR9 are activated by microbe-derived nucleic acids including double stranded RNA and CpG motif containing unmethylated DNA, respectively.

After the binding of corresponding ligands, TLRs activate MyD88-dependent and MyD88-independent signaling pathways, which are related to the production of inflammatory mediators, anti-microbial peptides and induction of acquired immunity to eradicate invading microorganisms. The downstream signaling has now been extensively studied, which should be referred to excellent reviews.

It is postulated that TLR4 and gut microflora-derived LPS contribute to the progression of liver fibrosis. Alcohol induces LBP and TLR4, and increases responsiveness to gut-derived endotoxin. Binding of LPS to CD14/TLR4 on KCs activates production of cytokines and oxidants, which leads to T cell recruitment, HSC activation and collagen production in the liver of patients with alcoholic steatohepatitis. The study of TLR4 to fibrosis progression was further extended to viral hepatitis C. A large patient cohort demonstrating TLR4 signaling in HSCs and endothelial cells, while the other type contains TLR4 intact KCs and TLR4 mutant HSCs and hepatocytes.
Patients with alcoholic cirrhosis had a significantly decreased endotoxin binding capacity in the liver. LPS is removed via several mechanisms, including molecules that bind LPS and prevent it from activating TLR4, enzymes that degrade the lipid A moiety to decrease its activity, and inactivation of LPS following uptake into the liver and spleen. Another mechanism for LPS neutralization is by serum lipoproteins, high-density lipoprotein (HDL), LDL, VLDL, and chylomicrons, apolipoproteins apoE and apoA-I. All of these mechanisms can chaperone endotoxin to hepatocytes, Kcs, or sinusoidal endothelial cells, resulting in clearance of LPS without significant inflammatory cell activation.

Due to its lipophilic structure, LPS also adheres to plasma lipoproteins, particularly HDL. HDL particles are multifunctional lipoprotein complexes that transport lipids and have several anti-inflammatory properties. Patients with alcoholic cirrhosis had a significantly decreased whole blood endotoxin-binding capacity together with decreased HDL plasma concentrations, which might result in an increase of the portion of unbound and, possibly more toxic, endotoxin. LBP is an acute phase protein induced by LPS, IL-6, and IL-1β. Interestingly enough, this protein has a bi-directional action on inflammation (pro-inflammatory and anti-inflammatory) induced by LPS. It usually catalyzes the transfer of LPS to CD14, and thus enhances the LPS-induced activation of monocytes, macrophages, and other immune cells. However, in the blood rich in HDL, LBP transfers LPS to HDL with an aid of apolipoprotein (Apo) A-I. Two experimental studies have shown that HDL administration reduced the effects of LPS on tumor necrosis factor-α production and systemic hemodynamics, restoring liver endothelial nitric oxide synthase activity and decreasing portal pressure. Incubation of whole blood with reconstituted HDL prevents LPS-induced tumor necrosis factor-α and interleukin-6 overproduction by monocytes of patients with cirrhosis.

Until now endotoxin binding and inactivating capacity of albumin have been relatively ignored. In a trial of stabilizing standard endotoxin by an addition of albumin, we happened to notice that albumin inhibits endotoxin activity in the chromogenic assay system. This observation has led us to hypothesize that albumin may act as a protective protein against endotoxemia. In our preliminary study, we first noted that 250 pg/mL endotoxin lost most of their activity in the presence of albumin at physiological concentrations. Another interesting result was that albumin inhibits LPS-stimulated IL-1 secretion in the macrophage culture system. We further noted that the capacity of albumin to bind exogenous 1H-labelled endotoxin decreased in plasma of cirrhotics. In patients with Child A and Child B cirrhosis, the plasma endotoxin inactivating rate was positively correlated to the endotoxin binding capacity of plasma albumin. Albumin has a protective effect against encephalopathy in advanced cirrhosis. Substances which require albumin binding-such as bilirubin, free fatty acids and organic anions markedly increase in the blood in this situation. The increase of these substances may limit endotoxin binding capacity of albumin. In Child C cirrhotics in whom albumin shows very low endotoxin binding capacity, additional microbial loads by acute infection may result in overwhelming endotoxemia and serious clinical results. Mechanisms of LPS clearance in the blood and LPS-induced inflammation are summarized in Figure 1.

How to evaluate BT clinically

As described above, plasma endotoxin assay has been mostly widely used. Despite the development of various new assay technique based on LAL test, there is no standard accepted method for clinical use. We have established chromogenic LAL test with kinetic analysis and compared various methods of plasma pretreatment, including the dilution and heating method and the perchloric acid method under the strict control by internal endotoxin standard. We have compared endotoxin-specific chromogenic substrate with the conventional chromogenic substrate and could not find out any superiority of the endotoxin-specific test for evaluation of BT. Both tests were well correlated to clinical course and considered to be useful markers. It should be noted that (1-3)-β-D-glucan powerfully co-stimulate cytokine production and systemic hemodynamics, restoring liver endothelial nitric oxide synthase activity and decreasing portal pressure. Although most quantitative LAL test reacts (1-3)-β-D-glucan and is not endotoxin-specific, both endotoxin from Gram-negative bacteria and (1-3)-β-D-glucan from fungus are microbial products which translocate from the intestine. They strongly co-stimulate innate immune system and induce the production of inflammatory mediators. The drawbacks of the tests are complexity of the measurement and difficulty in standardization. I could not recommend other endotoxin assay method with very low sensitivity. It was designed to detect endotoxemia with bacteremia but not suitable for detection of spillover endotoxemia in liver diseases. Endotoxin activity assay using a novel chemiluminescent assay will be evaluated for this purpose. I list up current detection methods of...
endotoxemia with their pros and cons in Table 1.

LBP can be evaluated as another useful surrogate marker of BT, although both endotoxin and LBP reflect only translocation of Gram-negative bacilli [4]. Elevated LBP levels in cirrhosis were related to pro-inflammatory state and haemodynamic derangement, which were shown to be ameliorated by intestinal decontamination with norfloxacin [132]. A prospective study in non-infected cirrhotics with ascites showed that increased serum LBP was the only factor independently associated with first severe bacterial infection in a multivariate analysis [133]. Detection of serum peptidoglycan, a polymer consisting of sugars and amino acids that forms the cell wall of gram-positive bacteria, has been considered as a marker of BT in an experimental model of hemorrhagic shock [4,134]. Recently, detection of bacterial DNA (bactDNA) by polymerase chain reaction has been proposed as a surrogate marker for BT, although both endotoxin and LBP reflect only translocation of Gram-negative bacilli [4]. Elevated LBP levels in cirrhosis were related to pro-inflammatory state and haemodynamic derangement, which were shown to be ameliorated by intestinal decontamination with norfloxacin [132]. A prospective study in non-infected cirrhotics with ascites showed that increased serum LBP was the only factor independently associated with first severe bacterial infection in a multivariate analysis [133]. Detection of serum peptidoglycan, a polymer consisting of sugars and amino acids that forms the cell wall of gram-positive bacteria, has been considered as a marker of BT in an experimental model of hemorrhagic shock [4,134]. Recently, detection of bacterial DNA (bactDNA) by polymerase chain reaction has been proposed as a surrogate marker for BT. It has been simultaneously detected in blood and ascites in 9 of 28 cirrhotics with culture-negative ascites [135]. Detection of bactDNA in biological fluids in experimental cirrhosis and ascites is associated with its simultaneous presence in MLNs [136]. Bellot et al. [137] reported that bactDNA (+) patients had significantly lower mean arterial pressure and systemic vascular resistance. The increase in hepatic venous pressure gradient after the test meal significantly correlated with serum bactDNA concentration.

Uniformity of analytical methods is needed to ascertain its real value in clinical setting [4].

**THERAPEUTIC APPROACH TO LIVER CIRRHOSIS BY MANAGEMENT OF THE GUT-LIVER AXIS**

Our hypothesis about the mechanism of endotoxemia and its consequences related to complications in advanced liver cirrhosis are shown in Figure 2. Gram-negative bacteria and endotoxins are more likely than other types of bacteria to stimulate tumor necrosis factor and cytokines that would lead to the production of nitric oxide (NO) [138]. Endotoxemia in relation to bacterial translocation, causes induction of NO synthase leading to increased vascular NO production, which is the primary stimulus for the development of vasodilatation and its accompanying clinical manifestations in cirrhosis [99]. Nitric oxide is also a potent inducer of increased membrane permeability in the vascular endothelium and intestinal mucosa, possibly contributing to bacterial translocation [28,99]. In patients with advanced cirrhosis, there may be a vicious cycle among endotoxemia, induction of NO and increased intestinal permeability, which may further induce derangement of the hyperdynamic circulatory status and renal failure. New clues to improving
prognosis of advanced liver cirrhosis may be found in better management of gut-liver axis.

Selective intestinal decontamination
Selective intestinal decontamination (SID) for management of complications of liver cirrhosis has a long and evolving history. At first, the word SID was not used but the trial to eliminate the endogenous source of gram-negative aerobic bacteria was reported early in 1982. Adachi et al.\(^\text{[39]}\) reported that oral administration of polymyxin B is useful in the treatment of hyperammonemia and endotoxemia in liver cirrhosis, as a poorly absorbed antibiotic and as an antiendotoxin agent. Similarly, Tarao et al.\(^\text{[47]}\) stated that paromomycin sulfate (2 g/d for 4 wk) is effective in the prevention of endotoxemia and the associated renal impairment in cirrhosis. Although the effect of the latter was not reproduced later in patients with alcoholic liver disease.\(^\text{[140]}\)

Long-term use of norfloxacin (400 mg/d, mean follow-up period 6.4 ± 0.6 mo) has been reported to eliminate aerobic *gram-negative bacilli* from the fecal flora without significant changes in other microorganisms throughout the study.\(^\text{[141]}\). A double blind, placebo-controlled trial evaluating its efficacy in cirrhotics who recovered from an episode of SBP, revealed a significant reduction of SBP recurrence by 68% at one year of follow-up.\(^\text{[141]}\). In cirrhotic patients with low ascitic fluid protein concentrations (≤ 1 g/dL) or hyperbilirubinemia (> 2.5mg/dL), long-term prophylactic treatment with norfloxacin was also effective in the prevention of the first episode of SBP (1.8% vs 16.9%)\(^\text{[142]}\). However, these promising results were followed by the problem of quinolone-resistant disease.\(^\text{[142,143]}\). Prior antibiotic therapy and norfloxacin prophylaxis is confirmed to increase the risk of carriage of methicillin-resistant Staphylococcus aureus.\(^\text{[144]}\). After that, primary prophylaxis of SBP has been targeted to high-risk patients. When cirrhotics with low protein ascitic levels (< 1.5 g/dL), advanced

### Table 1 Detection methods of endotoxemia

| Name of the test (manufacturer) | Pro | Con |
|--------------------------------|-----|-----|
| LAL test | Good marker of BT | Not specific, react βd-Glucan, plasma preparation difficult |
| Chromogenic substrate assay | Good marker of BT available for both end-point assay and kinetic assay | Not specific, react βd-Glucan PCA method: poor endotoxin recovery plasma pretreatment reagent currently unavailable |
| LAL Coatest, S-2423 | Good marker of BT available for both end-point assay and kinetic assay | Not specific, react βd-Glucan, not available now |
| EndosafePTS (Charles River Lab) | Good marker of BT handy and quick | Not specific, react βd-Glucan (Concomitant use of Endosafe PTS glucan assay may be necessary for specificity) |
| LAL chromogenic endpoint assay | Good marker of BT available for both end-point assay and kinetic assay | Not specific, react βd-Glucan |
| Hycult Biotech Mini-LAL-assay (Hycult Biotechnology) | Good marker of BT available for both end-point assay and kinetic assay | Not specific, react βd-Glucan |
| ToxinSensorTM Chromogenic LAL Endotoxin Assay (GenScript) end-point method | Endotoxin-specific available for both end-point assay and kinetic assay | PCA method: poor endotoxin recovery plasma pretreatment reagent currently unavailable |
| Endospecy (Seikagaku Corporation) | Endotoxin-specific available for both end-point assay and kinetic assay | New PCA method: plasma pretreatment reagent currently unavailable |
| Turbidometric assay | Endotoxin-specific | Unable to detect spillover endotoxemia in cirrhosis |
| Recombinant factor C (rFC) system assay | Endotoxin-specific | Very few reports, usefulness for liver disease unclear |
| Endotoxin activity assay | Received FDA clearance rapid diagnostic for endotoxin activity in human whole blood. Higher EAA™ levels are correlated with a higher risk of mortality, as well as an increasing risk for developing sepsis | Addition of methylprednisolone decreased the EAA levels. Indirectly endotoxin assay to reflect the primed state of polymorphonuclear leukocytes |

LAL: Limulus amebocyte lysate; FDA: Food and Drug Administration.
liver failure (Child-Pugh score $\geq 9$ points with serum bilirubin level $\geq 3$ mg/dL) or impaired renal function were selected, primary prophylaxis with norfloxacin reduced the incidence of SBP, delayed the development of hepatorenal syndrome, and improved survival.$^{[146]}$

Rifaximin is a minimally absorbed oral antimicrobial agent that is concentrated in the gastrointestinal tract$^{[146]}$. It has broad-spectrum in vitro activity against gram-positive and gram-negative aerobic and anaerobic enteric bacteria, and has a low risk of inducing bacterial resistance$^{[147-149]}$. Given its pharmacologic characteristics this drug has been used in the treatment of hepatic encephalopathy. Rifaximin has been compared with neomycin$^{[150]}$, paromomycin$^{[151]}$, and lactulose$^{[152]}$, showing similar results in both clinical improvement and reducing blood ammonia$^{[153]}$. Recently its effect on advanced liver cirrhosis as SID agent has been intensively studied. Vlachogiannakos et al$^{[154]}$ reported that a 4-wk rifaximin regimen significantly ameliorated endotoxemia and lowered hepatic venous pressure gradient in patients with decompensated alcohol-related cirrhosis. Kalambokis et al$^{[148]}$ noted that rifaximin treatment reduced cardiac output and increased systemic vascular resistance, glomerular filtration rate and natriuresis, in association with decreases in plasma renin activity, endotoxin, IL-6, and TNF-α levels. These data supported that intestinal decontamination with rifaximin improved systemic hemodynamics and renal function in patients with advanced cirrhosis. Decrease of ascitic neutrophil count in cirrhotic patients with sterile ascites$^{[155]}$ and improvement of thrombocytopenia$^{[156]}$ were also reported by the same group. Dănulescu et al$^{[157]}$ further reported that rifaximin causes a significant decrease in ascitic neutrophil count, producing a decrease in SBP frequency and improvement of life in cirrhotic patients with refractory ascites.

Several recent studies evaluated its effect on brain function based on the concept of gut-liver-brain axis. Rifaximin is associated with improved cognitive function and endotoxemia in minimal hepatic encephalopathy (MHE), which is accompanied by alteration of gut bacterial linkages with metabolites without significant change in microbial abundance$^{[158]}$. A significant improvement in cognition including working memory and inhibitory control, and fractional anisotropy without effect on MD or MR spectroscopy, through modulation of fronto-parietal and subcortical activation and connectivity was seen after open-label rifaximin therapy in MHE$^{[159]}$.

**Probiotics**

Probiotics, lactose-fermenting *Lactobacilli* and *Bifidobacteria*, have been reported to stabilize mucosal barrier function and modulate the gut microflora, suppressing pathogenic microbial growth$^{[70]}$. They acidify the gut lumen, compete with pathogenic bacteria for nutrients, and produce antimicrobial substance$^{[70,160,161]}$. Administration of VSL#3, a probiotic combination
of eight strains of *Lactobacilli, Bifidobacteria* and *Streptococcus*, has been reported to reduce oxidative/nitrosative stress parameters in patients with alcoholic liver cirrhosis\(^{[162]}\). Cirrhotic subjects receiving *Escherichia coli Nissle* for 42 d showed an effectiveness in the restoration of normal colonic colonization and a trend of significant lowering of the endotoxia and improvement of liver functions evaluated by Child-Pugh score\(^{[163]}\). Stadlbauer et al\(^{[164]}\) proved that probiotics restore neutrophil phagocytic capacity in cirrhosis, possibly by changing IL-10 secretion and TLR4 expression, warranting larger randomized controlled and mechanistic studies. Probiotics are able to decrease the permeability of the intestinal wall, and decrease bacterial translocation and endotoxemia in animal models as well as in clinical studies, which is extremely important in the prevention of complications of liver cirrhosis and infection after liver transplantation\(^{[165]}\). Probiotics could limit oxidative and inflammatory liver damage and, in some situations, improve the histological state\(^{[165]}\). Recent meta-analysis could not confirm that probiotics are effective to hepatic encephalopathy\(^{[166]}\). Further clinical trials are needed to know an ideal probiotic therapy for this purpose\(^{[166]}\).

**Symbiotics**

Symbiotic treatment was also associated with a significant reduction in endotoxia\(^{[164]}\). The Child-Pugh functional class improved in nearly 50% of cases\(^{[164]}\). Symbiotic preparation consisting of 4 freeze-dried, non-urease-producing lactic acid bacteria and four fermentable fiber, Symbiotic 2000\(^{[16]}\), was effective to patients with liver cirrhosis and minimal hepatic encephalopathy\(^{[167]}\). Symbiotic treatment for 30 d significantly increased the fecal content of non-urease-producing *Lactobacillus* species, which was associated with a significant reduction in blood ammonia and endotoxin\(^{[167]}\). An improvement in Child-Pugh class occurred in 47% of patients receiving symbiotic preparation, compared with 29% or 8% of patients receiving fermentable fiber alone or placebo, respectively\(^{[167]}\). For the prevention of infections, this symbiotic regimen (Symbiotic 2000\(^{[16]}\)) was more effective than fiber alone in reducing the incidence of bacterial infections in liver transplant recipients\(^{[168]}\). Additionally, Wan et al\(^{[169]}\) reported that taurine and oat fiber achieved an additive inhibitory effect on intestinal endotoxin release in a rat liver ischemia/reperfusion model, which might be an effective approach for the treatment of intestinal endotoxia.

**Prebiotics**

Lactitol and lactulose are synthetic non-absorbable disaccharides. They remain undigested until they reach the large bowel, where they are metabolized by colonic bacteria, generating acetic and lactic acids. The resulting lower pH may inhibit urease-producing intestinal bacteria and promote the growth of non-urease-producing *Lactobacilli*\(^{[170]}\). Chen et al\(^{[171]}\) reported that lactitol increased beneficial bacteria, such as *Bifidobacteria* and *Lactobacilli* with a significant decrease in plasma endotoxin levels in patients with chronic viral hepatic diseases.

**New cocktails and others**

Current approaches for hepatic encephalopathy include the use of non-absorbable antibiotics (i.e., neomycin, paromomycin, metronidazole, or rifaximin) and non-absorbable disaccharides\(^{[70]}\). Probiotics may be a promising therapeutic option in the management of hepatic encephalopathy\(^{[167,172-174]}\), although we need more clinical studies to get a final conclusion\(^{[168]}\). Some authors have shown that probiotics may positively modulate the gut microflora, reducing the amount of bacterial ammonia reaching the portal vein\(^{[70]}\). The long-term oral administration of *Enterococcus faecium SF 68* was equally effective as lactulose and its effect on mental status persisted longer than lactulose\(^{[172]}\). Oral intake of *Bifidobacterium longum* plus fructooligosaccharides for 90 d was also effective in biochemical and neuropsychological tests of cirrhotics with minimal hepatic encephalopathy\(^{[175]}\).

**CONCLUSION**

It has been proposed that a “leaky gut” may be the cutting edge for the passage of toxins, antigens or bacteria into the body, and may play a pathogenic role in advanced liver cirrhosis and its complications. More attention should be paid to the role of intestinal bacteria and bacterial products in the field of hepatology. The usefulness and the limitations of selective intestinal decontamination should be more clearly defined. Rifaximin may be promising. However, more judicious combinations of probiotics and prebiotics should be explored. Infusion of albumin or HDL in addition to endotoxin adsorption may be theoretically effective for intractable endotoxemia. Moreover, adequate management of the gut-liver axis is even effective for prevention of fibrosis in alcoholic and nonalcoholic steatohepatitis. This seems to be a radical therapy to decrease liver cirrhosis itself. Readers interested in the topics are recommended to read recent excellent reviews\(^{[4,70,71,82,103,108]}\). The research in these fields may open a new possibility in the next decade.

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