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Infection as a Trigger for Portal Hypertension

Christian J. Steib Julia Schewe Alexander L. Gerbes

Department of Medicine II, University Hospital LMU Munich, Liver Center Munich, Munich, Germany

Key Words
Kupffer cell · Hepatic stellate cell · Portal pressure · Liver cirrhosis · Toll-like receptors

Abstract
Background: Microbial infections are a relevant problem for patients with liver cirrhosis. Different types of bacteria are responsible for different kinds of infections: *Escherichia coli* and *Klebsiella pneumoniae* are frequently observed in spontaneous bacterial peritonitis or urinary tract infections, and *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* in pulmonary infections. Mortality is up to 4-fold higher in infected patients with liver cirrhosis than in patients without infections. ***Key Messages:*** Infections in patients with liver cirrhosis are due to three major reasons: bacterial translocation, immune deficiency and an increased incidence of systemic infections. Nonparenchymal liver cells like Kupffer cells, sinusoidal endothelial cells and hepatic stellate cells are the first liver cells to come into contact with microbial products when systemic infection or bacterial translocation occurs. Kupffer cell (KC) activation by Toll-like receptor (TLR) agonists and endothelial sinusoidal dysfunction have been shown to be important mechanisms increasing portal pressure following intraperitoneal lipopolysaccharide pretreatment in cirrhotic rat livers. Reduced intrahepatic vasodilation and increased intrahepatic vasoconstriction are the relevant pathophysiological pathways. Thromboxane A_2 and leukotriene (LT) C_4/D_4 have been identified as important vasoconstrictors. Accordingly, treatment with montelukast to inhibit the cysteinyl-LT_1 receptor reduced portal pressure in cirrhotic rat livers. Clinical studies have demonstrated that activation of KCs, estimated by the amount of soluble CD163 in the blood, correlates with the risk for variceal bleeding. Additionally, intestinal decontamination with rifaximin in patients with alcohol-associated liver cirrhosis reduced the portal pressure and the risk for variceal bleeding. ***Conclusions:*** TLR activation of nonparenchymal liver cells by pathogens results in portal hypertension. This might explain the pathophysiologic correlation between microbial infections and portal hypertension in patients with liver cirrhosis. These findings are the basis for both better risk stratifying and new treatment options, such as specific inhibition of TLR for patients with liver cirrhosis and portal hypertension.

Infections in Patients with Liver Cirrhosis

Bacterial infections are a relevant problem in patients with liver cirrhosis. One meta-analysis showed a risk for mortality up to 4-fold for patients with liver cirrhosis suf-

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E-Mail karger@karger.com
www.karger.com/ddi

Christian J. Steib, MD
Department of Medicine II, University Hospital LMU Munich
Campus Grosshadern, Liver Center Munich, Marchioninistrasse 15
DE–81377 Munich (Germany)
E-Mail christian.steib@med.uni-muenchen.de

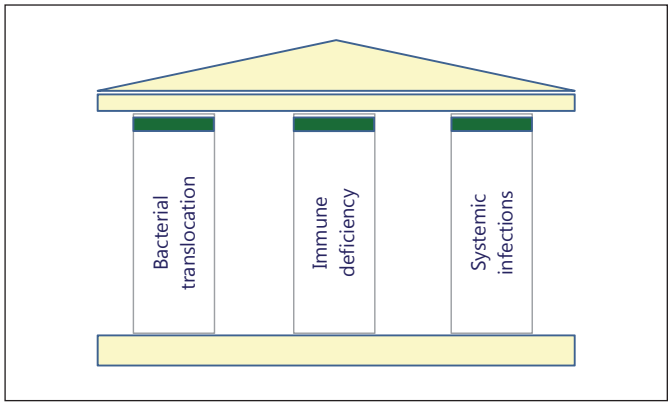

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Fig. 1. The three columns represent the most common reasons for infections in patients with liver cirrhosis. Patients with liver cirrhosis often suffer from bacterial infections. One postulated mechanism is bacterial translocation due to reduced bowel motility and increased intestinal permeability. Furthermore, patients with liver cirrhosis have immune deficiency, and the incidence of systemic infections is also high in these patients.

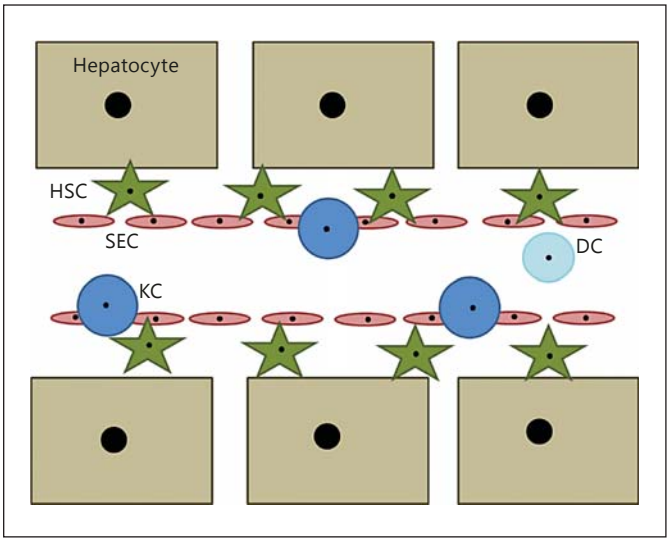

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Fig. 2. Sinusoidal architecture of the liver. Blood flow from the portal vein enriches the sinusoidal compartments of the liver. On the forefront of the sinusoidal lumen there are KCs and SECs. They are embedded in the HSCs, which have the potential for contraction because they have myosin and actin filaments. Also, some migrated DCs can be found in the layer of nonparenchymal cells, which are surrounded by hepatocytes – the parenchymal cells.

fering from infection [1]. Different kinds of infections are relevant in patients with liver cirrhosis: spontaneous bacterial peritonitis (SBP), urinary tract infections and pulmonary infections. Common pathogens for SBP are *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*; for urinary tract infections *E. coli* and *K. pneumoniae*, and fur pulmonary infections *S. pneumoniae* and *Mycoplasma pneumoniae* are frequently involved (see table 1). There are three relevant reasons why patients with liver cirrhosis suffer more often from infections: bacterial translocation, immune deficiency and an increased incidence of systemic infections, as presented by the three columns in figure 1.

Table 1. Frequent kinds of infections and common pathogens in patients with liver cirrhosis

Kind of infection	Common pathogens
SBP	*E. coli* *K. pneumoniae* *P. aeruginosa* *S. pneumoniae*
Urinary tract infections	*E. coli* *K. pneumoniae*
Pulmonary infections	*S. pneumoniae* *M. pneumoniae*

Bacterial Translocation

Bacterial translocation is supposed to be a common problem in patients with liver cirrhosis. Three main mechanisms influence bacterial translocation: the intestinal microbiome, the intestinal barrier and the intestinal lymphatic tissue. The intestinal microbiome is altered in patients with liver cirrhosis due to malnutrition, bile acid deficiency, potential alcohol consumption and an increasing number of multiresistant bacteria. Additionally, the intestinal barrier is altered in patients with liver cirrhosis. Alterations are due to potential alcohol ingestion and proinflammatory cytokines, e.g. TNF-α. Via the intestinal lymphatic tissue a relevant amount of microbial products reaches the portal vein in patients with liver cirrhosis. This amount of microbial products is higher in patients with liver cirrhosis compared to healthy volunteers [2–4]. Impaired clearance of the lymphatic tissue aggravates bacterial translocation. The microbial products from the intestinal tract reach the sinusoidal lumen and first meet the nonparenchymal liver cells, like Kupffer cells (KCs), sinusoidal endothelial cells (SECs), hepatic stellate cells (HSCs) and migrated dendritic cells (DCs; fig. 2).

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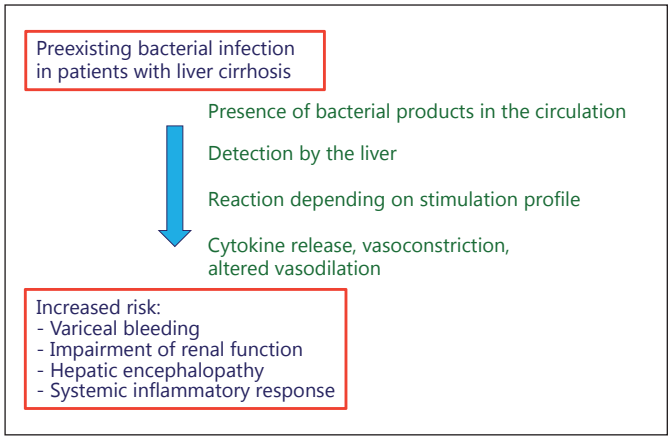

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Fig. 3. Proposed pathophysiology for an increased risk of complications in patients with liver cirrhosis. Bacterial products from the systemic circulation reach the liver and are detected there. A reaction depending on the stimulation profile is then generated. The following cytokine release resulting in vasoconstriction and altered vasodilation increases the risk for variceal bleeding, impairment of renal function, hepatic encephalopathy and systemic inflammatory response.

Portal Hypertension

The pathophysiology of portal hypertension underlies a wide range of different mechanisms. However, there are two major mechanisms: increased splanchnic blood flow and increased intrahepatic resistance. The intrahepatic resistance is influenced by the altered liver architecture (cirrhotic nodules and scars) and by the intrahepatic contraction. Intrahepatic contraction is dependent on both the production of and response to vasoconstrictors and vasodilators. In cirrhotic livers the production of and response to vasoconstrictors is increased. The production of and response to vasodilators, however, is diminished. Therefore, the intrahepatic contraction is a dynamic component and might be targeted by pharmacologic treatment.

Infections and Portal Hypertension

The current concept of the interaction between infections and the liver is as follows. There is a preexisting microbial infection in patients with liver cirrhosis meaning pathogens are present in the systemic circulation. Pathogens are detected by receptors on liver cells, e.g. Toll-like receptors (TLRs). A reaction in the liver will occur depending on the stimulation profile. Cytokine release, vasoconstriction due to an increased production of vasoconstrictors and altered vasodilatation lead to an increased risk for complications of liver cirrhosis, such as variceal bleeding, impairment of renal function, hepatic encephalopathy and systemic inflammatory response (fig. 3). Experimental data has shown that 24-hour treatment with lipopolysaccharide (LPS) in cirrhotic rats induced liver sinusoidal endothelial dysfunction. This was shown by a decreased vasodilatory response to acetylcholine and a decreased endothelial NOS phosphorylation following LPS pretreatment. The inhibition of inducible NOS prevented liver endothelial dysfunction [5]. In another study, LPS-induced intrahepatic endothelial dysfunction was prevented by simvastatin treatment, indicating that statins might be a treatment option for liver protection during endotoxemia [6].

Experimental data has also focused on vasoconstrictors. Different vasoconstrictors are metabolites of the arachidonic acid pathway. Arachidonic acid is metabolized to prostaglandin (PG) G_2 by cyclooxygenase and to 5-HPETE by 5-lipoxygenase. PGG_2 is further degraded to PGH_2, thromboxane (TX) A_2 and its stable degradation product TXB_2, and on the other side to PGD_2, E_2, F_2 and I_2. 5-HPETE is degraded to leukotriene (LT) A_4 and consecutively to B_4 or the cysteinyl (Cys)-LT C_4, D_4 and E_4. In the cirrhotic liver the vasoconstrictor TXA_2 and Cys-LT C_4 and D_4 have been identified as the most relevant [7–17].

KC Activation in Cirrhotic Rat Livers

KCs can be activated by TLRs [18, 19]. Zymosan is supposed to activate TLR2 and TLR6. The acute administration of zymosan in the isolated liver perfusion system increased portal perfusion pressure by about 3-fold. This increase could be reduced by additional indomethacin administration [11]. In cirrhotic rat livers portal perfusion pressure increased impressively following infusion of zymosan; however, most interestingly, intraperitoneal pretreatment with LPS enhanced this increase of portal perfusion pressure to a higher degree [12]. Additional gadolinium chloride pretreatment for the blockade of KCs reduced LPS/zymosan-induced increase of portal perfusion pressure [12]. This indicates that KCs are important players in the TLR-mediated increase of portal perfusion pressure. In parallel with portal hypertension, TXB_2 and Cys-LT efflux into the effluent perfusate increased [12]. In further studies the effect of portal perfusion pressure increase following TXA_2 analogon infusion

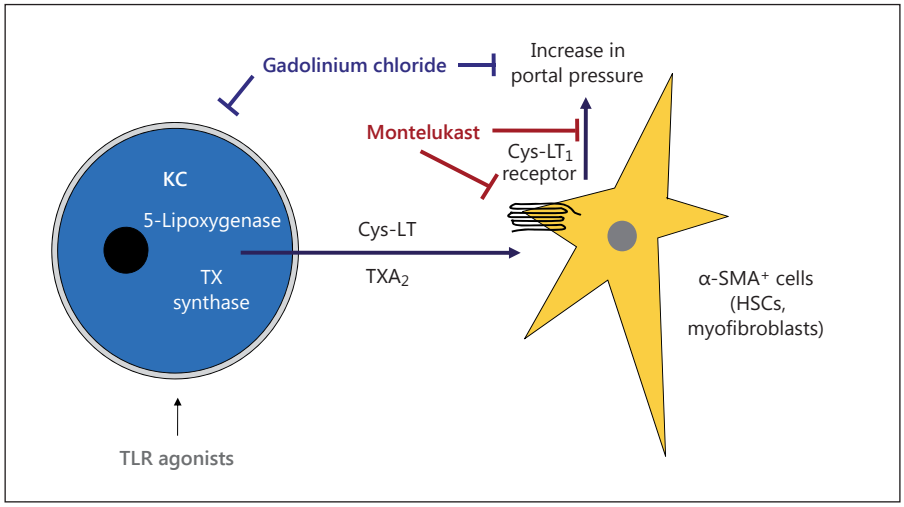

Fig. 4. Proposed pathophysiology of KC activation and portal pressure increase. Agonists of TLRs, e.g. different pathogens during systemic infections or in the context of bacterial translocation, activate KCs, which increases TXA_2/B_2 production and LT C_4/D_4 production via cyclooxygenase and TX synthase or 5-lipoxygenase. The activation of HSCs via the TX receptor or the Cys-LT_1 receptor presumably leads to a contraction of HSCs and, therefore, an increase in portal pressure. Vice versa blockade of KCs by gadolinium chloride or blockade of the Cys-LT_1 receptor by montelukast reduces portal hypertension.

was enhanced by additional infusion of LTC_4 [13]. This indicates that both arachidonic acid metabolites act independently and additively. While TXA_2 inhibition would influence thrombocyte aggregation, LT inhibition presumably has no obvious effects for patients with liver cirrhosis. Inhibition of Cys-LT_1 receptor might therefore be a reasonable therapeutic strategy for patients with portal hypertension; experimental data ruled out the beneficial effect of Cys-LT_1 receptor inhibition with montelukast in rat liver cirrhosis (fig. 4) [13].

A further therapeutic approach investigated in experimental studies might be the administration of rifaximin for intestinal decontamination. It has been shown that pretreatment with rifaximin reduced portal pressure in mice with bile duct ligation (BDL)-induced liver cirrhosis [20]. It has also been shown that the TLR4-dependent cross-talk between stellate cells and endothelial cells was inhibited in mice with liver fibrosis [20].

Therefore, KCs seem to play an important role in TLR-mediated production of vasoconstrictors and the associated increase of portal pressure. The effector cells of intrahepatic contraction are presumably the HSCs. Relevant mechanisms of intrahepatic contraction Rho kinases have been evaluated [13, 14, 21–25]. The importance of Rho kinase for HSC contraction was first described by studies with isolated cultured HSCs. During their activation and transformation to the myofibroblastic phenotype, HSCs acquire contractile potential. Such studies investigated how Rho kinase affects the resting tone of HSCs and vasoconstrictor-induced HSC contractions. Under resting conditions, the Rho kinase inhibitors Y27632 and HA1077 relaxed rat HSCs in collagen matrix assay [26, 27]. HSC activation is associated with excessive proliferation and transformation to the contractile phenotype [28], which confers hypercontractility to the intrahepatic vasculature resulting in increased intrahepatic vascular resistance [21]. HSC-specific blockade of Rho kinases might therefore be another promising therapeutic strategy in TLR-dependent portal hypertension [24].

Immune Deficiency

Beside TLR-mediated intrahepatic contraction due to bacterial translocation and due to an increased risk for bacterial infections, immune deficiency plays an important role in patients with liver cirrhosis. Different mechanisms underlie the pathophysiology of immune deficiency in cirrhosis, including the deficiency of bactericidal and opsonic activities [29], altered monocyte function and defective chemotaxis [1, 2]. Furthermore, PGE_2 has been shown to be an important mediator of immunosuppression in liver cirrhosis [30]. Increased PGE_2 levels have been found in plasma of patients with liver cirrhosis and acute decompensation of liver function [30]. Macrophages exhibited reduced bacterial killing when incubated with plasma from patients with acutely decompensated cirrhosis. This effect was reversed by additional treatment of the macrophages with an antagonist to prostanoid E receptors 1–3 and prostanoid D_2 receptor. Furthermore, mice with BDL-induced cirrhosis were injected with group B streptococcus intraperitoneally. Bacterial load in the peripheral blood was elevated in BDL animals compared to sham animals, and this effect was reversed

by indomethacin treatment. Indomethacin treatment also improved survival in BDL animals. Furthermore, the authors gave a potential treatment option. Treatment with albumin (20%) resulted in lower levels of blood bacteria in BDL animals exposed to bacteria. In parallel, lower levels of PGE_2 have been measured. The authors therefore hypothesized that PGE_2 is an important mediator of immunosuppression in liver cirrhosis and this effect could be attenuated by albumin treatment [30].

Clinical Studies

In accordance with the pathophysiological data, there is substantial evidence in clinical studies that the immediate administration of antibiotics is essential in patients with variceal bleeding [31–35]. Antibiotics should be administered together with vasoactive drugs before endoscopic therapy when the event of variceal bleeding is suspected or obvious. The earlier the pharmacological treatment starts, the better for the patient. The choice of the antibiotic therapy is dependent on the local resistance spectrum. A recent study investigated the different effects of different vasoactive drugs. It has been demonstrated that hemostatic effects and safety did not differ significantly between terlipressin, somatostatin and octreotide as adjuvants to endoscopic treatment in patients with acute gastroesophageal variceal bleeding [36].

Furthermore, new markers haven been evaluated in clinical studies in the context of infection as a trigger for portal hypertension. One of these markers is soluble (s) CD163. sCD163 can be measured in the peripheral blood via ELISA and is supposed to indicate KC activation. Interestingly, the cumulative bleeding hazard correlated with the level of sCD163 [37]. sCD163 might therefore be a new clinical tool for patients with portal hypertension to better predict the risk of variceal bleeding. Rifaximin has been tested in patients with alcoholic cirrhosis as a new therapeutic strategy. It was presumed that portal hypertension was attenuated by intestinal decontamination. Indeed, the hepatic venous pressure gradient decreased after 4 weeks of rifaximin treatment [38]. A second study showed that patients under treatment with rifaximin more rarely suffered from variceal bleeding compared to a control group [39].

To better understand the mechanisms and the relevance of bacterial translocation in liver cirrhosis, blood from the portal vein might be very helpful. However, there are several limitations to obtaining blood from the portal vein. Some studies have investigated blood samples taken during transjugular intrahepatic portosystemic shunt (TIPS) procedures, comparing blood samples from the hepatic vein and the portal vein. In one study it was found that cirrhotic livers retain the capacity for clearance of bacterial endotoxin from the portal venous blood and that TIPS implantation attenuates this clearance [40]. In this study, LPS-binding protein was measured by limulus amebocyte lysate assay [41]. In another study bacterial DNA was measured in blood from the hepatic vein and the portal vein during a TIPS procedure [42]. No transhepatic gradient of bacterial DNA was observed. The authors concluded that no major hepatic elimination of bacterial DNA occurs in advanced liver diseases. Furthermore, the authors demonstrated that bacterial DNA was unrelated to a panel of markers of inflammation and without relation to portal pressure [42]. These divergent results underline the difficulty in investigating and better understanding the mechanisms and consequences of bacterial translocation in liver cirrhosis.

Another clinical study investigated the role of nonselective β-blockers to better understand the pathophysiology and as a possible treatment option to reduce bacterial translocation. Nonselective β-blockers are primarily known to reduce portal pressure by reducing portal inflow. Otherwise, they have also been investigated in more detail under the rationale of reducing bacterial translocation [43]. The permeability index correlated with the hepatic venous pressure gradient and, under β-blocker therapy, not only was the hepatic venous pressure gradient decreased, but so too was intestinal permeability. Abnormal gastroduodenal permeability and intestinal permeability was associated with a reduced risk for variceal bleeding, but no effect on mortality has been observed [43].

Another important issue in considering bacterial translocation in cirrhotic patients is to take into account the use of proton pump inhibitors. There are different data on proton pump inhibitors and the risk for development of SBP [44–46]. A recent study found that proton pump inhibitors were more frequently used in SBP patients than in controls, but did not influence the prognosis in SBP [47]. In addition, overuse of proton pump inhibitors was encountered in one third of cirrhotic patients [47]. It is unclear whether proton pump inhibitors increase the risk for spontaneous bacterial infection; however, the indication for proton pump inhibitor therapy should be made very thoroughly, in particular in patients with liver cirrhosis.

In the context of bacterial translocation and portal hypertension probiotics have also been evaluated for pa-

tients with liver cirrhosis. Probiotics are live microorganisms that produce a beneficial effect to the host when administered in an adequate dose. Probiotics are not drugs, but rather combinations of bacteria. In adjunctive therapy a beneficial effect has been observed in patients receiving propranolol and in addition VSL#3 as a probiotic therapy, with response rates to propranolol being subsequently improved [48]. On the other hand, probiotic administration alone did not show effects on portal pressure in compensated [49] and decompensated cirrhosis [50].

Summary and Perspectives

The issue of bacterial infections in patients with liver cirrhosis and in particular for portal hypertension is a relevant problem and has been focused on even more during recent years. In addition to the existing data in humans and in animals, further research is essential. In particular, research is needed to distinguish between the relevance of bacterial translocation and systemic infections like urinary tract infections and pulmonary infections. Nonparenchymal liver cells might potentially be used for risk profiling in future studies and defined cytokine profiles might help to better understand the pathophysiology and also help to detect risk constellations earlier. Antibiotic therapy, especially continuous antibiotic therapy, brings the risk of development of resistant bacteria. The formation of an increasing number of resistant bacteria has been observed during recent years. Therefore, a strong selection of patients is needed who will in particular profit from continuous antibiotic prophylaxis (e.g. for spontaneous bacterial infections). This means a better risk stratification is important. Furthermore, precise antibiotic therapy for identified constellations has to be considered in the future, for which profiling and better diagnostic tools might be helpful. Furthermore, the development and testing of new therapeutic agents for the treatment of patients with liver cirrhosis in the future is essential. Inhibitors of the 5-lipoxygenase pathway or inhibition of its metabolites and development and testing of TLR antagonists or specific TLR blocking agents will be necessary to improve treatment for patients with liver cirrhosis and portal hypertension in the future.

Disclosure Statement

The authors have nothing to disclose.

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