

# Gut-Liver Axis Links Portal Hypertension to Acute-on-Chronic Liver Failure

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## Keywords

Portal hypertension · Systemic inflammation · Acute-on-chronic liver failure, ACLF · Microbiome · Bacterial translocation

## Summary

Acute-on-chronic liver failure (ACLF) is considered a distinct syndrome in patients with liver disease, with systemic inflammation playing a central role. Portal hypertension (PHT) is also aggravated by inflammation and may subsequently impact the course of ACLF. PHT is more than just an increase in portal pressure in the portal venous system; it aggravates the course of liver disease and, thus, also facilitates the development of acute decompensation and ACLF. A critical mechanistic link between PHT and ACLF might be the gut-liver axis, which is discussed in this review.

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## Introduction

Advanced chronic liver disease (ACLD, a term that is used similarly to cirrhosis) represents a major cause of morbidity and mortality worldwide [1]. In 2010, cirrhosis was responsible for 1,029,042 deaths (ca. 2% of total global deaths) [2]. By 2013 this figure had increased to 1.2 million deaths [3], not taking into account the more than 750,000 liver cancer deaths, mainly as a result

of liver cirrhosis [2]. The age-standardized mortality rate of cirrhosis in Europe ranges between 10% in Western Europe, 18% in Central Europe and 20% in Eastern Europe [2]. Acute decompensation (AD) and its progression to acute-on-chronic liver failure (ACLF) are major causes of death due to cirrhosis [4]. Cirrhosis with AD and ACLF are also responsible for 14,544,000 disability-adjusted life years worldwide [2]. Once AD has developed, 15% of hospitalized patients will further develop ACLF, and of those, 40% will die within 90 days [5]. ACLF is characterized by the presence of organ failure(s) in acutely decompensated patients [6], but is a very dynamic syndrome with a considerable percentage of patients who do recover [7]. Different predisposing factors (e.g. genetics, epigenetics) and precipitating events (e.g. active alcoholism, infections, bleeding) have been discussed to be involved in the development of AD and in its progression towards ACLF [5]. The substantial inter-individual differences in the predisposition to develop AD and its progress to ACLF with high mortality remain largely unexplained and form the subject of an ongoing multicenter European study, the PREDICT study (NCT03056612).

In Europe, the main etiology of decompensated cirrhosis is alcoholic liver disease [8]. Probably due to the highly stigmatized status of this etiology, there is a striking imbalance between the burden of cirrhosis and prioritization of treatments and research efforts, which is why they are often overlooked in novel research and treatment foci in universities and hospitals. Interestingly, in 2015, only 7 out of 72 studies worldwide in the field of liver disease investigated cirrhosis and only 1 focused specifically on the syndrome of ACLF [9]. Moreover, as ACLF has been characterized only recently in the CANONIC study [5], optimal management strategies remain to be defined.

## Portal Hypertension and Acute Decompensation

A hallmark of worsening prognosis in liver cirrhosis is the development of portal hypertension (PHT), mostly referred to as clinically significant portal hypertension (CSPH) [10–12] characterized by a hepatic venous pressure gradient (HVPG) of  $\geq 10$  mm Hg. This is defined as increased pressure in the portal vein, the direct vascular connection between the gut (splanchnic organs) and the liver [10–12]. PHT triggers many complications, including development of collaterals (varices) with significant risk for gastrointestinal bleeding, ascites, and hepatic encephalopathy. Importantly, bacterial translocation is increased in the presence of PHT (fig. 1). This is likely related to 2 different mechanisms: On the one hand, venous congestion and splanchnic neoangiogenesis, due to the increased pressure in the portal vein, induce impaired microcirculation and lead to increased permeability in the gut [13]. On the other hand, ascites formation, induced by PHT, seems to be another pathogenic condition of bacterial translocation. Bacterial translocation is of relevance as it is considered one – if not the most – important trigger of AD and ACLF, as it leads to continuous activation of the immune system and chronic systemic inflammation [14–17].

Several direct or indirect consequences of PHT can predispose patients to development of AD and ACLF. Increased abdominal pressure due to ascites or atelectasis of the lung, due to hydrothorax, can facilitate the development of infections such as spontaneous bacterial peritonitis (SBP) or pneumonia, which, together with the increased risk of aspiration in the presence of hepatic encephalopathy (HE), might exacerbate to ACLF with a very poor prognosis [18–21]. However, the hemodynamic derangements in PHT might also predispose to ACLF. Impaired cardiac function (the so-called cirrhotic cardiomyopathy), usually occurring in severe PHT with hyperdynamic circulation, and diminished effective arterial blood volume with consecutive low mean arterial pressure predispose to inadequate cardio-hemodynamic compensatory response after the insult and therefore promote the development of ACLF, as shown for renal failure and hepatorenal syndrome (HRS) in different large retrospective studies [22–24]. Interestingly, a small prospective study from India demonstrated that hemodynamic derangements in cirrhotic patients increase the risk of mortality in ACLF [25]. In these patients, the risk of severe morbidity and mortality after variceal bleeding is considerable and associated with significantly worse outcome [25]. However, variceal hemorrhage no longer represents a major predisposing or precipitating factor for the development of ACLF [5]. A potential reason for this is the successful implementation of BAVENO recommendations for primary [26] and secondary prophylaxis [27] of variceal hemorrhage and adoption of early transjugular intrahepatic portosystemic shunt stent (TIPS) [28, 29] strategies in high-risk patients in clinical practice. Thus, optimized management of variceal bleeding has improved the outcome and considerably reduced its contribution as a trigger for ACLF development [28, 29]. Indeed, PHT predisposes and predicts survival in cirrhotic patients. However, while serum biomarkers of chronic inflammation will decrease in most

patients after successful TIPS treatment of PHT, these proinflammatory biomarkers remain of independent predictive value for subsequent mortality in cirrhotic patients – even after successful lowering of the portal pressure by TIPS [17, 30]. Thus, cirrhotic PHT predisposes to ACLF directly through hemodynamic derangements and indirectly through its complications.

## Gut-Liver Axis and Liver Diseases

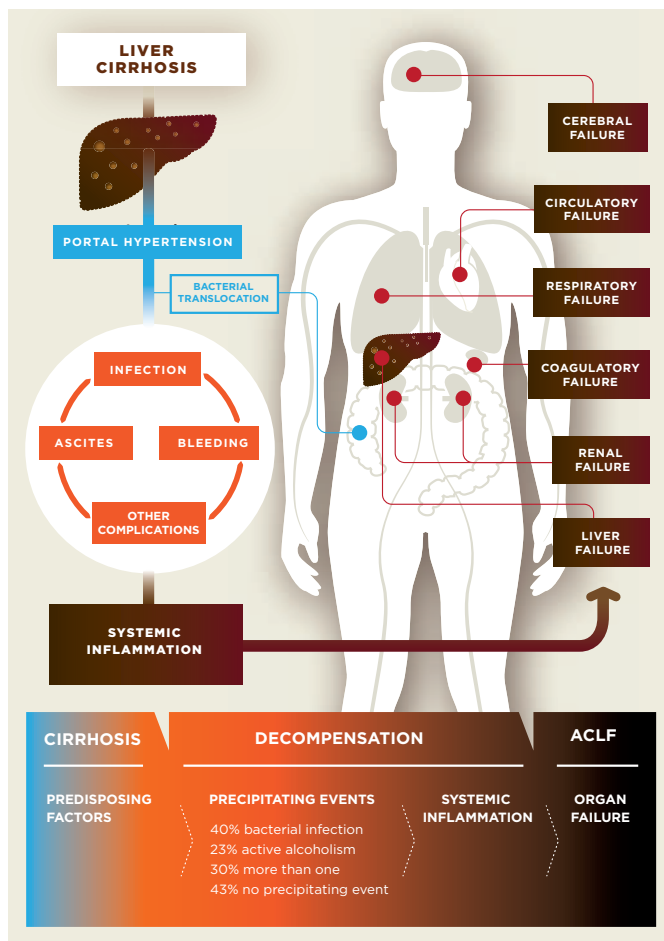
The gut microbiota and the gut barrier – together with systemic inflammation – and in particular a microbial translocation trigger sustain and further escalate the development of AD and progression to ACLF [4, 14].

The gut microbiota represents the largest pool of genetic material in the body with high metabolic activity. Every human being harbors at least  $4 \times 10^{13}$  colonizing microbial cells [31] and more than 10 million non-redundant microbial genes in their gut [32, 33]. There is sufficient evidence that changes in microbiota impact on the progression of liver disease (elegantly summarized in recent reviews [33–35]) and that profound changes in the microbiota occur with the development of liver cirrhosis [36], while underlying mechanisms remain not yet fully explored. There are key players in this interaction, such as an impaired epithelial barrier, in cirrhosis known as ‘leaky gut’ [33–35], with bacteria or metabolites entering into the portal blood circulation, interacting with immune cells and reaching the hepatic microcirculation, where they interact with nonparenchymal and parenchymal liver cells. The liver also secretes bile acids, which in turn modify the intestinal microbiome and, also, act as signaling molecules between the cirrhotic liver, the gut microbiota, and the intestine [37].

The human microbiota is currently one of the most dynamic research fields and description of functionality and role of the gut microbiome in human health and disease has seen great progress, facilitated by technological and methodological advances [38].

The factors influencing the gut microbiome may be classified into 3 categories: host-intrinsic, host-extrinsic, and environmental. Moreover, the microbiome state feeds back upon itself and, thereby, contributes to compositional variation between individuals. Clearly, these categories overlap and many factors are also associated to each other.

However, the effect size of the different known technical and biological microbiome covariates seem to be in the single digit percent [38]. This could be due to the fact that associations of individual taxa are more relevant than global compositional shifts, or that the gut microbiome’s intrinsic ecological dynamics and interactions are largely unknown, in part due to a lack of longitudinal data [38]. Nevertheless, the current total quantification of external factors to microbiome variation is probably in the range of 10–15% and, thus, of sufficient effect size to be considered in clinical studies, as even some individual factors can confound associations. This likely remains true even if one extends the definition of MWAS to ‘microbiome-wide association studies’ by also including other data types, such as metatranscriptomic or metabolomic readouts [39].



**Fig. 1.** Complications of liver cirrhosis are mainly due to portal hypertension, while bacterial translocation seems to play an important role as the trigger.

Therefore, microbiome data should be interpreted with great caution. Nevertheless, bacterial translocation is a well-accepted and reproducible process in cirrhosis and has been shown to be an essential driver in the development of complications.

### Bacterial Translocation and Systemic Inflammation

While the etiology of cirrhosis may vary, the microbiome-liver interaction is largely etiology-independent [33]. Only a small percentage (10–30%) of chronic liver diseases progresses to cirrhosis, but due to its high mortality [2, 3] it is of the utmost importance to assess any presence of cirrhosis and PHT – primarily by noninvasive methods, such as transient elastography [40]. At this stage, dysbiosis and bacterial translocation are frequent phenomena, which also determine the development of decompensations in cirrhosis [34], already described in the 1990s [41]. Especially, when PHT is present (increased pressure in the portal vein and the mesenteric veins collecting blood from the splanchnic organs to the liver), complications arise [42]. A TIPS is the most effective treatment of PHT and yet, even after this procedure, many patients de-

velop complications of liver disease [43, 44], especially due to the spillover of inflammation with resulting development of ACLF as shown by recent data [5, 45, 46]. Additionally, it was found that the presence of ascites, as a sign of decompensation, determines the composition of the circulating microbiome in the portal vein compared to the hepatic vein, right atrium, and peripheral venous blood, and that specific circulating microbiome members correlate with inflammatory markers [47]. It has been established that a specific microbiome phenotype (so-called enterotype) induces pathologies also in hepatic functions [32, 33], and that a wide range of microbial effectors (e.g. fungi [48]) may be involved in the development of systemic inflammation.

Systemic inflammation has been shown to cause complications in different chronic diseases. Especially in decompensated liver cirrhosis, it may result in a fatal outcome. The role of systemic inflammation in patients receiving TIPS has been studied in many scenarios [15–17, 45, 49–50]. There is a clear relationship between PHT, hyperdynamic circulation, development of complications, ACLF, and outcome [51]. Interestingly, systemic inflammation can also be reduced by TIPS, underlining the hypothesis that PHT drives systemic inflammation [17, 30, 47, 50]. However, C-reactive protein and white blood cell count may not be suitable early markers of systemic inflammation. In a recent study, patients in which levels of inflammatory markers were higher in the hepatic vein than in the portal vein developed more organ failure and showed a worse outcome [45]. Therefore, while systemic inflammation might be induced by PHT, it persists in some patients even when PHT has been effectively treated and may lead to ACLF.

### Decompensation and Response to Treatment

It is already well accepted that the presence of ascites defines decompensation in patients with liver cirrhosis [52]. However, in patients with decompensated cirrhosis, a subgroup exists with a very high short-term mortality [4]. These patients usually experience acute deterioration of their underlying liver disease, often due to a precipitating illness induced by infection, gastrointestinal bleeding, active alcoholism, or medications. These situations are called AD episodes and usually require hospital admission [4]. In 15% of these patients the clinical situation deteriorates and ACLF occurs [5].

In patients with liver cirrhosis and its complications, there are currently no specific strategies to prevent the development of AD and progression towards ACLF [53]. In general, the treatment options are relatively limited and mostly focus on the symptom rather than the pathogenesis of the liver disease. At this late stage, it is difficult to address the cause of liver injury, as the main focus is to keep the patients alive [53]. Studies have shown that in this collective, a variety of treatment options are needed to treat liver cirrhosis and that the drug response has been very heterogeneous [53]. One reason for these unsatisfactory results might be that the role of the gut microbiome has not been addressed properly. The gut microbiome, apart from its pathogenetic role, possibly also influences

the effect of medication, either due to the drug metabolism or due to the drug's effect on the microbiome metabolites [54, 55]. Interestingly, 25% of all nonantibiotic drugs change at least one gut species and this figure is most likely underestimated [56]. To date, in liver cirrhosis there is only 1 study showing the effect of drugs, namely proton pump inhibitors, on gut microbiota changes [57], possibly facilitating the development of alcoholic liver disease. However, the microbiome and its impact on ACLF remains a largely unexplored research area.

### Poorly Absorbable Antibiotics as Gut-Liver Axis Intervention

Whether rifaximin, a poorly absorbable antibiotic, prevents progression in the early stages of alcoholic liver disease is currently under investigation in GALAXY [58].

Several studies have suggested continuous antibiotic treatment as prophylaxis against the development of specific decompensation events, such as SBP, either as primary prophylaxis in specific conditions or as secondary prophylaxis after an episode of SBP [59]. In the specific clinical situation of a variceal bleeding, the prophylactic administration of antibiotics might prevent AD and ACLF, and it has been shown to improve survival. Here, the use of antibiotics, mainly third-generation cephalosporines and fluoroquinolones, is recommended [59]. Another important issue, which needs to be addressed, is the development of resistance in bacteria in these patients towards widely used antibiotics. Besides these problems, the role of prophylactic treatment in patients with decompensated cirrhosis has been documented once again in a large multicenter trial, which assessed the role of norfloxacin in patient survival [60]. Norfloxacin is a poorly absorbed antibiotic, which is very effective in changing the gut microbiota. Its role was analyzed decades ago in animal models. However, the published data were conflicting, with some studies reporting significant improvement in vascular function and PHT, whereas others did not observe significant effects. Nevertheless, all studies have shown a decrease in bacterial translocation to the mesenteric lymph nodes. While in a recently published, large, randomized placebo-controlled trial the effects of norfloxacin on decompensation and survival were beneficial, many study patients, nevertheless, developed decompensation and died despite norfloxacin administration [61]. In the subgroup analysis, the survival benefit was more pronounced. For the treatment of HE, rifaximin, another poorly absorbed antibiotic, has been approved. Many studies have tested the effect of rifaximin on the progression of liver disease, especially due to alcohol. However, the findings remain unconvincing to date. In some studies, rifaximin showed a major preventive effect [62, 63], while in others, this effect could not be determined or was only minor [64, 65]. Thus, while there is some evidence that some patients might benefit from rifaximin, a better selection and stratification of patients is required in the clinical setting.

### Albumin as Attenuation of Inflammation

Human albumin (HA), an important plasma protein synthesized in the liver, has been used for decades as a marker of liver dysfunction. Parenchymal extinction with progression of fibrosis and liver disease is also associated with hypoalbuminemia, which might play a specific predisposing role in the development of ACLF. During development of AD and progression to ACLF, the quality of HA in liver cirrhosis greatly deteriorates, as shown by the portions of reversibly and irreversibly oxidized HA, which correlate with ACLF grade and survival [46]. Hypoalbuminemia and the quality of albumin contribute to increased cytokine levels and others proinflammatory mediators (e.g. PGE<sub>2</sub>), which predispose for ACLF in cirrhosis [66–68]. While albumin treatment has been used in different clinical situations for years, the patient benefit remains under discussion. In a small number of scenarios, a clear benefit can be noted, such as in HRS, which basically is a functional renal failure in cirrhosis, in the prevention of HRS when SBP is present, and in the prevention of post-paracentesis-induced circulatory dysfunction [59, 69]. These scenarios require more or less infusion of HA. Regarding HA administration, adherence to guidelines is good, however, a significant use of albumin outside of recommended indications persists [70]. These data suggest that the 'gut' feeling of clinicians favors the use of albumin and that its use depends on the experience of the clinician adapting the HA treatment to their patient's needs. However, most attempts to prove benefits of HA treatment in other scenarios resulted in controversial findings, and HA in non-SBP infections might not bring any benefit at all [71, 72]. A large trial in Italy evaluating long-term administration of albumin in patients with AD showed an improvement in survival and a decrease in complications, such as hepatic encephalopathy, renal dysfunction, etc. [73]. Other smaller studies suggest the opposite and have even reported severe adverse events, e.g. pulmonary edema patients with pneumonia, however, albumin administration still prevents HRS and new infections [74]. To date, all attempts to stratify patients have failed and new tools to predict a response to HA are urgently required, as, on the one hand, it is an expensive and human-derived treatment agent, and, on the other hand, it could lead to complications.

### Conclusion

Development of PHT in chronic liver disease predisposes to development of complications and progression to ACLF. Especially, the gut microbiome and translocation of bacteria and bacterial components (e.g. pathogen-associated molecular patterns (PAMPs)) play an important role in the development of systemic inflammation. These systemic proinflammatory states, aseptic and septic, might persist after efficient treatment of PHT fueling immune dysregulation and further triggering the development of organ failures and thereby ACLF. Microbiome- and inflammation-directed treatments are emerging as promising targets to amelio-

rate PHT and normalize individual cytokine profiles and specific immune-dysbalanced states in ACLF.

## Acknowledgment

The authors thank S. Dentler for critical reading.

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## Disclosure Statement

JT is supported by Deutsche Forschungsgemeinschaft (SFB-TRR57 P18), Cellex Foundation, the European Union's Horizon 2020 Research and Innovation Programme (No. 668031) and Societal Challenges (health, demographic change and well-being (No. 731875)). TR has received grant support by Abbvie, Boehringer-Ingelheim, Gilead, MSD, and Philips Healthcare.

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