The concept of acute-on-chronic liver failure (ACLF) was introduced in 1995 and gradually has received more attention since the introduction of albumin dialysis [1]. In its early definition, it was described as a rapid deterioration of liver function in a patient with previously well-compensated liver disease, usually provoked by an acute insult. This insult could be either primarily hepatotoxic or indirect due to variceal bleeding or infection [2]. The primary hepatotoxic causes of ACLF differ among different geographical areas. In Western countries, acute alcoholic liver disease is common, and reported prevalence varies between 39% and 92% [3,4]. In Asia, mostly hepatitis B reactivation or the intake of hepatotoxic drugs is reported in the literature [5,6]. On the Indian subcontinent, a high incidence of hepatitis E superinfection was proposed in the etiology of ACLF [7].

The definition of ACLF is a matter of ongoing debate. In 2008, the Asian Pacific Association for the Study of the Liver proposed a consensus guideline defining the concept of ACLF [8]. In that paper, liver failure was defined as the development of jaundice and coagulopathy, complicated by ascites or encephalopathy or both within a time frame of 4 weeks. Remarkably, in this expert consensus definition, the precipitating event leading to ACLF was obligatory hepatic in origin. Thus, this definition excluded liver failure elicited by infection or gastrointestinal bleeding. Alternatively, in the recent literature in the West, ACLF is regarded more as a systemic complication of chronic liver disease since its clinical presentation is almost invariably accompanied by hemodynamic alterations, kidney failure, multi-organ failure, and inflammatory changes mimicking severe inflammatory response syndrome (SIRS) [2,3].

ACLF differs from chronic hepatic decompensation (CHD) in two key elements. First, the development of liver failure and end-organ dysfunction in ACLF is much faster than in CHD. In the literature, this period ranges from 2 to 12 weeks [2,3,8,9]. Second (and maybe of more importance), in ACLF, there is still a chance of recovery of liver function. This is illustrated by clinical data in our prospective clinical cohort study, in which 54% of patients with ACLF survived hospitalization, and transplant-free survival rates in time matched those of comparable patients with CHD [3].

The high prevalence and mortality rates associated with ACLF make it an important health-care issue and, owing to the use of the MELD (Model for End-Stage Liver Disease) scoring system, renew interest in liver transplantation. In reported literature, short-term mortality rates vary from 46% to 89% [10]. Mortality in ACLF is closely related to the development of SIRS in patients, irrespective of the severity of liver disease [3,11].
**Pathophysiology of acute-on-chronic liver failure**

Three main mechanisms are currently proposed as key elements in the development of ACLF: immune dysfunction, intestinal bacterial translocation, and circulatory dysfunction (Figure 1). We will discuss each of these elements separately and point out important interactions in the context of ACLF.

**Innate immune dysfunction**

*The innate immune system and Kupffer cells*

The innate immune system serves as a first-line defense mechanism against bacteria and toxins. It generates a non-pathogen-specific inflammatory response after stimulation with highly conserved antigens, such as lipopolysaccharides (LPSs). The main effector cells of the innate immune system are phagocytic cells, such as macrophages, neutrophils, and monocytes. The main cellular components of the innate immune system within the liver are the Kupffer cells. The liver is extremely important in innate immunity since Kupffer cells represent 80% to 90% of the tissue macrophages in the human body [12]. The strategic location of Kupffer cells within the lumen of the liver sinusoids and the anatomical location of the liver as a first-line station for bacteria and toxins derived from the gut further stress the importance of the liver as a strategic immunological organ.

*Classic mechanism of Kupffer cell activation*

Several basic scientific data support the concept of innate immune dysfunction on the cellular and molecular level in ACLF. The main orchestrator of immune dysfunction in liver disease has proven to be the Kupffer cell...
Kupffer cells in healthy liver exert many roles: they intervene in hemoglobin degradation, phagocytize bacteria and damaged cells, serve as antigen-presenting cells, and eliminate toxins such as ethanol [12,13]. Importantly, they interact intensively with other cells such as immune cells, sinusoidal endothelial cells, hepatocytes, and stellate cells, especially once they are activated. Kupffer cells are activated by many different stimuli through Toll-like receptors (TLRs). This form of Kupffer cell activation is considered the classic pathway of Kupffer cell activation into so-called M1 proinflammatory macrophages [14]. TLRs recognize multiple highly conserved pathogen-associated molecular patterns (PAMPs) and damage-associated molecular pathways (DAMPs). The most common pathway of Kupffer cell activation is considered the classic pathway of Kupffer cell activation into so-called M1 proinflammatory macrophages [14]. TLRs recognize multiple highly conserved pathogen-associated molecular patterns (PAMPs) and damage-associated molecular pathways (DAMPs).

Effects of classic Kupffer cell activation

Upon activation, Kupffer cells produce a great variety of inflammatory mediators such as cytokines, chemokines, oxygen-derived free radicals, eicosanoids, and lysosomal and proteolytic enzymes [10,12,13,18]. The massive release of local proinflammatory cytokines such as interleukin (IL)-1, IL-6, IL-17, IL-18, and tumor necrosis factor-alpha (TNFα) and the release of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 are considered causative in the subsequent development of SIRS and
compensatory anti-inflammatory response syndrome (CARS) in acute and acute-on-chronic liver failure because of the overflow of these cytokines into the systemic circulation [25]. Among the proinflammatory cytokines, TNFα has been most intensively studied since it is first released and correlates well with the overall severity of liver injury [26]. Cytokine release by Kupffer cells induces important leukocyte recruitment within the liver microvasculature and parenchyma. This is mediated in part by production of chemoattractants such as IL-8 and by expression of adhesion molecules such as ICAM-1 (intracellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) on sinusoidal endothelial cells in response to liver injury [27]. This further leads to the production of oxidative stress and proteolytic enzymes, enhancing hepatocyte apoptosis and necrosis in liver disease. Kupffer cells are also responsible for the transformation of quiescent stellate cells into activated myofibroblasts, which drive the intrahepatic microcirculation. Furthermore, activated Kupffer cells produce vasoactive substances such as endothelin-1 (ET-1), thromboxane A2, nitric oxide (NO), and prostaglandins, thereby establishing a direct link between immune activation and hepatic microcirculatory dysfunction [28]. Further evidence for this link is provided by a recent study demonstrating increases in portal hypertension in response to intra-peritoneal LPS injection in rats [29].

**Alternative activation of Kupffer cells**

On the other hand, Kupffer cells can be alternatively activated by cytokines such as IL-4 and IL-10, which are produced by Th2 cells and other innate immune cells such as basophils. Upon alternative activation, they further differentiate into M2 phenotype macrophages [30]. These M2-type macrophages exert mainly anti-inflammatory effects through mediators such as transforming growth factor-beta [31].

**Mechanisms of innate immune dysfunction in acute-on-chronic liver failure**

The mechanisms of innate immune dysfunction in liver cirrhosis and alcoholism are numerous. First, Kupffer cells are bypassed through multiple intra- and extrahepatic shunts in cirrhosis. Second, decreased liver protein synthesis generates defects in complement production, resulting in reduced opsonization capacity in chronic liver disease. Additionally, deficiency of albumin in patients with cirrhosis is common. Albumin is known to have important detoxifying qualities such as scavenging free radicals and LPSs [10]. Third, in cirrhosis, there is evidence for a dysfunctional and hyporesponsive state of the innate immune system, a phenomenon that is known as immune paralysis [10,32]. This was also recently revealed in patients with ACLF [33]. The phenomenon of immune paralysis has been illustrated in the 2007 study of Lin and colleagues [32]: patients with Child-Pugh class C cirrhosis were shown to suffer from downregulation of HLA-DR expression, directly hampering the mononuclear cell antigen-presenting capacity. On the other hand, the 2006 study by Tazi and colleagues [34] revealed an increased TNFα production after stimulation of monocytes by LPS in patients with advanced cirrhosis. Interestingly, two other previously mentioned studies obtained opposite results in their patient groups, so these findings remain a matter of debate [32,33]. A similar debate regards the phagocytic capacity of neutrophils in liver disease. Some studies suggested increased radical and elastase production in response to bacterial challenge as well as increased phagocytosis in portal hypertensive rats [35-37]. Other studies demonstrated phagocytic capacity impairment in patients with alcoholic cirrhosis [38]. Globally, experimental results point toward an overall activated state of the innate immune system in chronic liver disease and an overproduction of harmful substances such as free radicals and liver parenchymal injury as a consequence. This has been nicely illustrated by the use of gadolinium chloride in animal trials, depleting the liver of Kupffer cells. Kupffer cell-depleted rats showed substantially less liver damage after partial liver resection, LPS challenge, and alcohol- and acetaminophen-induced liver injury [15,39-41]. Moreover, TNFα levels have been shown to be significantly elevated in patients with advanced cirrhosis, further revealing the activated state of the immune system [33]. On the other hand, the activated immune cells appear to be dysfunctional, paralyzed, and energy-depleted, making patients susceptible to infections, as demonstrated by clinical data. These findings seem to be exacerbated in the context of ACLF, resulting in an exaggerated SIRS and a defective CARS, a phenomenon known in the literature as immunological dissonance [25,33]. The additional adverse effects of alcohol on immune function, especially on TLRs and cytokines, have been extensively studied [18-20,22,42-44]. However, this topic is beyond the scope of our review.

**Role of natural killer cells and natural killer T cells**

Recently, interest has arisen for other components of the innate immune system: the natural killer (NK) cells and the NK T cells. Although their role in ACLF has not yet been clearly elucidated, they obviously play an important role in many experimental models of liver injury, such as alcoholic liver disease, viral hepatitis, and autoimmune liver disease [45]. Furthermore, both NK and NK T cells are activated by bacterial toxins and bacterial superantigens and display hepatotoxicity through secretion of proinflammatory mediators such as TNFα. However,
anti-inflammatory markers, such as interferon-gamma, also are expressed by NK cells upon activation [46]. Future research will need to reveal the role of NK cells in the specific context of ACLF.

**Innate immune dysfunction in acute-on-chronic liver failure on the clinical level**

The presence of innate immune dysfunction in ACLF can be deduced from several observations in the context of ACLF, chronic liver disease, and alcoholism. The first evidence comes from clinical observations: infection is the reason for hospital admission in 15% to 35% of patients with cirrhosis, and 15% to 35% of the patients develop nosocomial infections in comparison with 5% to 7% in the general population [10]. Also, roughly one third of patients with advanced cirrhosis and culture-negative ascites exhibit bacterial DNA in circulation, which is closely correlated to the presence of intrahepatic and systemic endothelial dysfunction [47,48]. Furthermore, a large majority of patients with ACLF display sepsis-like characteristics such as the SIRS (Table 1) [3].

**Therapeutic strategies**

Many strategies have been attempted, with variable success, to modify or attenuate the immune response in acute, chronic, or acute-on-chronic liver disease. The application of corticosteroids in severe acute alcoholic hepatitis is well established [49]. Recently, more evidence has been generated regarding the beneficial effects of pentoxifylline, an inhibitor of TNFα, in the treatment of not only severe alcoholic hepatitis but also advanced cirrhosis [50,51]. The beneficial effect of TNFα monoclonal antibodies in severe alcoholic hepatitis is still controversial because, in one study, this was associated with higher infection and mortality rates [52]. Currently, a lot of scientific effort is put into targeting of innate immunity with TLR agonists and antagonists, but it is still unclear whether this is beneficial in the treatment of patients with liver disease [53].

**Intestinal bacterial translocation**

**Definition and prevalence of intestinal bacterial translocation**

Bacterial translocation is defined as the migration of viable microorganisms from the gut lumen to the mesenteric lymph nodes (MLNs) or extra-intestinal sites [54]. It seems to be of importance in cirrhosis and ACLF for two reasons. First, in patients with cirrhosis, bacterial translocation from the gut is a well-known source of life-threatening infection, such as spontaneous bacterial peritonitis. This represents an acute event in chronic liver disease, which in some patients results in ACLF. Second, bacterial translocation is thought to induce and perpetuate the previously mentioned activated state of the innate immune system [55]. Bacterial translocation has proven to be increased in experimental animal models of cirrhosis or portal hypertension and in human disease [47,56-60]. Bacterial translocation has been demonstrated especially by removal and culture of MLNs. Recently, bacterial DNA measurement in blood samples has proven to be a reliable, non-invasive, and probably more sensitive surrogate marker for translocation of viable bacteria in cirrhosis [48,60]. The prevalence of bacterial translocation is closely related to the severity of liver disease. For instance, bacterial translocation to MLNs has been demonstrated uniquely in animal models of cirrhosis in the presence of ascites [58]. Furthermore, in a large study in humans, only the Child-Pugh class and not the degree of portal hypertension was a predictive factor for the prevalence of bacterial translocation, suggesting that liver dysfunction might be more crucial in the development of bacterial translocation than portal hypertension in itself [57]. In that study, the prevalence of bacterial translocation increased according to the Child-Pugh classification: 3.4% in Child A, 8.1% in Child B, and 30.8% in Child C cirrhotic patients. However, this concept was challenged in two earlier experimental studies, in which acute (2-day) portal hypertension induced bacterial translocation in partial portal vein-ligated rats without liver disease [56]. In another study, bacterial translocation could also be demonstrated in rats with chronic portal hypertension, induced by means of partial portal vein ligation [59]. Moreover, it has been demonstrated that a second, acute injury to the system, such as hemorrhagic shock, further increases bacterial translocation from the gut, indicating its potentially important role in ACLF [59,61]. The presence of bacterial DNA in patients with cirrhosis proved, in a recent study, to be closely correlated to systemic and intrahepatic microcirculatory abnormalities [47]. This confirms once more the close link between circulatory dysfunction, immune dysfunction, and bacterial translocation in liver disease.
Mechanisms of bacterial translocation

Bacterial translocation originates from a large variety of dysfunctions within the gut-liver axis. Three key elements are recognized: changes in intestinal microflora, changes in intestinal permeability, and inadequate response of the gut immune system [55].

Changes in intestinal microflora

The microorganisms that are most frequently involved in bacterial translocation in humans are aerobic bacteria such as *Escherichia coli*, *Klebsiella* spp., *Staphylococcus aureus*, and *Enterococcus* [48]. In normal intestines, anaerobic bacteria, which rarely translocate, outnumber aerobic bacteria by 100:1 to 1,000:1 [62]. Anaerobic bacteria are known to prevent aerobic bacterial overgrowth. In patients with cirrhosis, bacterial overgrowth and changes in intestinal bacterial composition which were attributed largely to alterations in short-bowel motility and intestinal transit time have been documented [63,64]. This offers, in part, an explanation why aerobic bacteria are capable of translocating from the intestine in patients with cirrhosis.

Increased intestinal permeability

Another explanation for bacterial translocation is that patients with cirrhosis display increased intestinal permeability. In normal circumstances, intestinal permeability to water-soluble molecules is determined by the presence of tight junctions between intestinal epithelial cells [65]. These tight junctions restrict diffusion of molecules up to 2 kDa through the paracellular space, preventing migration of bacteria but also of bacterial endotoxins through the paracellular space, preventing migration [65]. In patients with cirrhosis, permeability was shown to be increased [66]. This is easy to conceive given the major morphological changes that occur in the intestinal epithelium in rat models of experimental cirrhosis. For instance, the viability of enterocytes in these rats was decreased, the villus fraction of enterocytes was heavily reduced, and (importantly) the cytoskeleton displays important morphological changes in cirrhosis [67]. The increases of intestinal permeability in cirrhosis have been attributed to the role of oxygen free radical damage, venous congestion, NO, and the direct effects of alcohol on the gut barrier [22,47,61,67].

Innate immune dysfunction in the gut

Finally, in normal circumstances, translocated microorganisms are easily phagocytized and removed by intestinal macrophages. However, in chronic liver disease, this bactericidal capacity is reduced, as discussed in the above sections.

Therapeutic strategies

Strategies to prevent translocation of aerobic bacteria from the gut have been successfully applied in patients with cirrhosis. For instance, antibiotics such as norfloxacain, known to selectively decontaminate the gut from Gram-negative bacteria, are used in variceal bleeding and the prevention of spontaneous bacterial peritonitis [68]. Furthermore, Tazi and colleagues [69] demonstrated that the hyperdynamic circulatory syndrome could be ameliorated by norfloxacin. Of interest, in a recent study in 30 patients with decompensated cirrhosis, a significant reduction of systemic and splanchnic plasma endotoxin levels but also a significant reduction of hepatic venous pressure gradient (HVPG) values were seen after intestinal decontamination therapy with rifaximin [70]. Other strategies such as probiotics and intestinal prokinetics such as propranolol were successful in animal trials but need further validation in humans [71].

Circulatory dysfunction

Innate immune dysfunction and bacterial translocation in the onset of ACLF result in major alterations on the macrocirculatory and intrahepatic microcirculatory levels (Figure 3).

Macrocirculatory level

On the macrocirculatory level, patients with ACLF display an aggravation of the hyperdynamic circulation, which is already present in advanced stages of compensated cirrhosis. Cardiac output is increased and peripheral circulation is diluted and hyporesponsive. Mean arterial blood pressure is decreased. On the splanchnic level, there is important arterial vasodilatation and portal hypertension, resulting in renal hypoperfusion. This further leads to water and sodium retention by activation of the renin-angiotensin II-aldosterone pathway and secretion of antidiuretic hormone [2]. In patients with cirrhosis, two important mechanisms have been recognized in the development and aggravation of portal hypertension. First, there is an increase of intrahepatic vascular resistance (IHVR), which can be attributed largely to alterations on the sinusoidal level [26]. Second, increased portal venous flow results from splanchnic hyperemia because of splanchnic arterial vasodilatation. Multiple factors have been implicated in these hemodynamic alterations.

Nitric oxide

An important role for NO is suggested on the peripheral as well as on the splanchnic level. NO is produced by two enzymes: one is an inducible isoform, iNOS, and the other is an endothelial constitutive isoform, eNOS. The latter proved to be the more important source of mesenteric artery NO overexpression in portal hypertension [72-74]. This upregulation of eNOS is thought to originate from shear stress increases related to increased splanchnic inflow [75]. Of interest in ACLF, an
upregulation of eNOS was seen in rats with bacterial translocation, correlating to circulating TNFα levels and severity of intrahepatic microcirculatory dysfunction [76].

**Microcirculatory level: stellate cells**

On the hepatic level, IHVR has proven to be partly static and partly dynamic [77]. This can be attributed to the microcirculatory system within the liver sinusoids. The presence of vascular thrombi, collagen deposits within the space of Disse, and nodular regeneration explain the static component in IHVR. However, portal hypertension can be partially reversed by use of vasoactive substances in liver perfusion studies [78-80]. This represents a dynamic and modifiable part of portal hypertension. The contractile elements within the hepatic microcirculation have proven to be the stellate cells. This has been demonstrated *in vitro*, in stellate cell gel contraction models, and in *in vivo* microscopy studies. Their distribution along the perisinusoidal space presents them with optimal sinusoidal constriction capacity. In normal liver, stellate cells are quiescent fat-storing cells. However, in the presence of liver injury, they become activated and proliferate into hepatic myofibroblasts. These myofibroblasts develop contractile properties through cytoplasmic processes and acquisition of multiple smooth muscle proteins [81]. Hepatic stellate cell contraction is mediated through both Ca²⁺-dependent and independent pathways [82]. Also, the role of sinusoidal endothelial cells in microvascular dysfunction in liver injury has been well established. Next to the production of vasoactive mediators such as NO and ET-1, sinusoidal endothelial cells are known to exert proinflammatory, proadhesive, and procoagulant properties upon activation [26]. Through close intercellular interaction with Kupffer cells and stellate cells, this vasomotor dysfunction is aggravated, probably promoting hepatocellular injury and a portal pressure increase in ACLF.
**Adrenal insufficiency**

Finally, in cirrhotic patients with renal failure or sepsis, a high incidence of adrenal insufficiency was found (range of 40% and 75%). Adrenal dysfunction seemed to be closely related to hemodynamic changes and mortality. The importance of this phenomenon and its potential therapeutic implications needs further validation [85].

**Therapeutic strategies**

ET-1 has been targeted in the experimental treatment of portal hypertension in multiple animal trials. Bosentan, for instance, a mixed ETα and ETβ receptor antagonist, has proven to be beneficial in the treatment of portal hypertension and portal hypertension-related complications such as variceal bleeding [86-88]. However, a recent European post-marketing study on the safety profile of bosentan in the treatment of pulmonary hypertension in 4,994 patients demonstrated elevated aminotransferases in 7.6% of patients over a period of 3,416 patient-years [89]. However, this toxic effect proved to be early and mostly mild and transient. Of interest, in two studies, bosentan was safely administered to 93 Child A cirrhotic patients suffering from portopulmonary hypertension [89,90]. Tezosentan, also a specific non-selective ET receptor antagonist, is also shown to limit liver injury in endotoxin-challenged cirrhotic rats [91]. In this respect, strategies to increase intrahepatic NO concentrations have been extensively studied. Replenishment of the defective eNOS enzyme has been obtained by NOS gene transfer in cirrhotic rats, attenuating portal hypertension [92]. Liver-directed NO donors have also been used with positive results in cirrhotic animal trials such as NO-releasing bile acids [93]. However, a recent randomized double-blind trial in humans failed to demonstrate portal pressure reduction in cirrhosis by means of NCX-1000, an NO-releasing derivative of ursodeoxycholic acid [94]. Also, statins are known to decrease the intrahepatic vascular tone in humans through an increase of hepatic NO production [95]. This is particularly important in ACLF since statins have been shown to improve outcome in sepsis, severe sepsis, and fatal sepsis [96,97]. Nitroflurbiprofen, an NO-releasing cyclooxygenase inhibitor,
was also proven to be beneficial in rat models of cirrhotic portal hypertension [80]. Studies in patients on this topic are lacking. Furthermore, experimental studies examining the beneficial effects in the specific context of ACLF need to be evaluated. The use of hydrocortisone in cirrhotic patients with documented adrenal insufficiency and septic shock is also under investigation. In a recent study by Arabi and colleagues [98] (2010), the administration of hydrocortisone in these patients resulted in higher shock reversal rates and less vasopressor use but significantly more gastrointestinal bleeding and ultimately comparable survival rates in comparison with the placebo-treated group.

Conclusions

ACLF is an important clinical challenge since it remains a highly prevalent, life-threatening disease with few therapeutic options at present. Treatment options are currently limited to supportive measures. However, ACLF has proven to be a potentially reversible complication of chronic liver disease. This emphasizes the need for a guided therapeutic approach, shifting the downward spiral seen in ACLF toward hepatic recompensation. The application of liver support devices for this indication has been disappointing, although further analysis in certain subgroups of patients might be warranted [99,100]. In recent years, knowledge regarding the pathophysiology of ACLF has largely increased. All research has pointed toward the interaction between innate immune dysfunction, bacterial translocation from the gut, and (micro) circulatory dysfunction as key players. This has resulted in several treatment modalities proven to be beneficial in animal or in vitro studies of liver disease. However, clinical studies in humans, especially in ACLF, are lacking. A second strategy to prevent ACLF-related death might lie in the early recognition of this syndrome. For example, since the development of ACLF coincides with the development of multi-organ failure, early recognition of kidney injury by use of biomarkers of renal function could be useful in predicting the development of ACLF in cirrhotic patients confronted with acute disease [49]. It is likely that combining an early recognition of the syndrome with a more pathophysiology-guided therapeutic approach will result in better survival rates of patients with ACLF, also reducing the need for liver grafts as an ultimate salvage therapy.

Competing interests

The authors declare that they have no competing interests.

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