Acute Decompensation and Acute-on-Chronic Liver Failure

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KEYWORDS

• Cirrhosis • Portal hypertension • Systemic inflammation • Metabolic dysfunction • Immune paralysis • Bacterial infection • Organ failure

KEY POINTS

- Acute decompensation is a heterogenous syndrome characteristic of end-stage liver disease.
- Throughout the various stages of acute decompensation, portal hypertension, systemic inflammation, and metabolic dysfunction are progressively aggravated.
- Acute-on-chronic liver failure is the final and most fatal stage of acute decompensation and is characterized by massive systemic inflammation.

CIRRHOSIS, ACUTE DECOMPENSATION, AND ACUTE-ON-CHRONIC LIVER FAILURE

Liver cirrhosis is the common end stage of all chronic liver diseases. Acute decompensation (AD) and its maximal form acute-on-chronic liver failure (ACLF) are a major cause of death in these patients.[1–3] Accounting for 14,544,000 disability-adjusted life-years worldwide, cirrhosis has become a major health care problem.[4] AD is by far the main reason for repeated hospitalization in patients with cirrhosis.[5] Treatment of AD and ACLF primarily aims at organ support.[6,7] Therapies are therefore unspecific, difficult, and expensive, and the clinical risk assessment and stratification of these patients are gaining paramount importance.[8]

The main precipitants leading to the occurrence of AD are proven bacterial infections, severe alcoholic hepatitis, gastrointestinal bleeding with shock, and toxic encephalopathy.[9] The onset and severity of AD correlate with the extent of systemic inflammation (SI); hence, it is assumed that the precipitating insult must cross a certain threshold to cause AD.[8–10] Among the various stages of AD, pre-ACLF is the condition that precedes to ACLF.[11] AD and ACLF will become more severe upon precipitants

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with concomitant organ failure (OF), and in the case of multiple precipitants.[9] ACLF is now considered the most severe form of AD, but their clinical phenotype as well as their inflammatory signature differs notably. SI is the hallmark of both AD and ACLF.

DEFINITION AND PATHOPHYSIOLOGY OF ACUTE DECOMPENSATION

Four Phenotypes of Acute Decompensation

AD is very common in end-stage liver disease, and it encompasses a variety of decompensating events.[12] A decompensating event is defined as any of the following 4 events: ascites, gastrointestinal bleeding, hepatic encephalopathy, or bacterial infection.[13] The course of end-stage cirrhosis is complicated by these decompensating events, which occur in an unanticipated and repeated manner.[14] Bacterial infections often lead to further decompensation events.[15] Gastrointestinal bleeding is significantly associated with new onset of spontaneous bacterial peritonitis and other bacterial infections.[12] Therefore, in patients with ascites, gastrointestinal bleeding, or hepatic encephalopathy, a decompensation event may cause another within the course of the disease.[14,16,17] Once patients with cirrhosis develop a first episode of AD, the median survival drops from 12 to less than 2 years.[18,19] For patients, the transition from compensated to decompensated cirrhosis is a "prognostic watershed," and it spotlights the clinical significance of AD.[12]

Four Different Trajectories of Acute Decompensation

Stable decompensated cirrhosis

Because decompensated cirrhosis is a polymorphic and dynamic process rather than a steady state, a concise sequence of severity grades of AD has been proposed.[11] This classification comprises four distinguished stages. Stable decompensated cirrhosis (SDC) is characterized by complications of cirrhosis, lower SI, and the possibility of timely recompensation.[20–22] Patients with SDC are therefore not readmitted because of further AD events. OFs are very rarely observed in SDC; however, brain or liver dysfunction does occur in 23% and 14% of patients, respectively. In many instances, SDC is preceded or accompanied by bacterial infections, which resolve however, and the patients may return to the stage of recompensation. The 1-year mortality is 10% in SDC.[11]

Unstable decompensated cirrhosis

Unstable decompensated cirrhosis (UDC) is associated with significant portal hypertension (PHT), shows a remarkably increased incidence of bacterial infections, and thus spawns further decompensation events.[11,20,23] Upon AD at the initial hospital admission, UDC is characterized by the necessity of at least 1 readmission owing to further decompensation events, but ACLF does not occur in these patients. Although organ dysfunctions occur more often than in SDC (29%, 19%, and 16% for brain, circulatory, and liver dysfunction, respectively), OF are still not frequently observed in UDC. Patients with UDC have a 1-year mortality of 36%. Importantly, gastrointestinal bleeding is significantly more often observed in UDC than in pre-ACLF, which underlines the role of clinically significant PHT in UDC.[11]

Pre–acute-on-chronic liver failure

Pre-ACLF is defined as an episode of AD, during or upon which ACLF develops.[11] It is associated with significant SI, therefore distinguishing pre-ACLF from SDC and UDC. However, because the notion of pre-ACLF has been described in 2020, it is important to disambiguate that the past studies investigating SI did not explicitly mention the term pre-ACLF.[20,23] Pre-ACLF is clinically characterized with a significant increase

in renal dysfunction (23% compared with 7% in both UDC and SDC). Among the non-ACLF forms of AD, prognosis is worst in pre-ACLF patients, with a 1-year mortality of 67%.[11]

Acute-on-chronic liver failure

Patients who develop ACLF have OFs. This means that ACLF may be constituted by either any 2 nonrenal OFs, any non-renal OF together with brain dysfunction, or any cirrhotic patient with acute renal failure.[1] Further OFs are possible and will lead to a more severe ACLF grade. Varying definitions of ACLF have been proposed by the EASL (European Association for the Study of the Liver), NACSELD (North American Consortium for the Study of End-Stage Liver Disease), and APASL (Asian Pacific Association for the Study of the Liver), but all of them rely on clinical characteristics, including the deterioration of liver function in combination with OFs.[24–26] ACLF is a highly dynamic entity of AD, and complete deterioration may occur within days. This includes the "full-blown" clinical picture of multiorgan failure, and intensive care, including organ support, is often necessary. Among all ACLF stages, renal failure is observed most frequently, followed by liver and coagulation failure (56%, 44%, and 28%, respectively).[1] ACLF is associated with a 28-day mortality of 22% (ACLF-1) up to 77% (ACLF-3).[1,3,27,28]

Discrimination of Acute Decompensation from Acute-On-Chronic Liver Failure

The presence of 2 or more OFs in patients with cirrhosis, combined with signs of both hepatic and systemic inflammation (SI), defines the condition of ACLF.[8] Altogether, ACLF encompasses 6 entities of OFs: renal, cerebral, liver, coagulation, circulation, and/or respiratory OF. For each of these OFs, specific and concise thresholds have been defined, and the severity of ACLF is graded from 1 to 3, depending on the number of organ systems failing. Exceptions with less than 2 OFs that also constitute ACLF are (A) single kidney failure, since it was observed that patients with renal failure have a disproportional poor prognosis,[1] and (B) cerebral dysfunction together with any non-kidney OF. Considering these clear cutoffs, the pragmatic clinical diagnosis of ACLF is straightforward. Nevertheless, the presence of ACLF depends on the time and dynamic of decompensation. There is uncertainty whether kidney failure alone or single OF with kidney dysfunction is as relevant as 2 OFs, which is a matter of debate among the different societies. However, the CANONIC study, which defined ACLF based on the mortality, could be reproduced by different studies and even the PREDICT study.[1,8,9,11] Because in ACLF the most important issue is probably to improve survival, those effects are subject to further clinical research.

Pathophysiology of Acute Decompensation and Acute-On-Chronic Liver Failure

Portal hypertension

For the most part, decompensation events arise because of the existence of PHT. PHT is therefore a central element predisposing for AD and ACLF. In a nutshell, PHT is a condition of increased hydrostatic pressure in the portal vein. This state of hypertension leads to (A) a reflex dilation of splanchnic arteriolae, and via circulatory dysfunction to vasodilation of peripheral arteries[29]; (B) excessive collateral angiogenesis with the formation of esophageal, gastric, and rectal varices[30–32]; and (C) bacterial translocation owing to inflammation of the intestinal lymphatic tissue, dysfunctional intestinal innervation, and epithelial swelling, resulting in SI.[33–36] Importantly, significant bacterial translocation only occurs in cirrhotic PHT, and not in acute and/or noncirrhotic PHT.[37] As a consequence, gastrointestinal bleeding may occur because of the spontaneous rupture of a varix; ascites owing to hydrostatic pressure itself; or spontaneous bacterial

peritonitis owing to a leaky intestinal barrier. Because PHT links bacterial translocation and SI, it also predisposes to the occurrence of ACLF.[28] It is noteworthy that SI can also be reduced by transjugular intrahepatic portosystemic shunt (TIPS), which is another strong hint pointing at the link between PHT and SI.[38,39] Furthermore, because of its hemodynamic derangements, PHT is a necessity for ACLF, for example, in the case of cirrhotic cardiomyopathy, which might lead to circulatory failure, and diminished effective arterial blood volume, leading to hepatorenal syndrome.[24,28,40]

Systemic inflammation

Interestingly enough, C-reactive protein (CRP) and leukocytes as biomarkers of SI are higher in patients with pre-ACLF than in patients with unstable or SDC (**Fig. 1**).[11] It was shown that patients with AD and an increased neutrophil-to-lymphocyte ratio especially tend to develop ACLF and die.[41] It was further observed that elevated levels of interleukin-6 (IL-6), IL-1RA, and HNA2 in patients with AD were independently associated with development of ACLF within 28 days.[23] IL-1α, IL-1β, plasma renin, and copeptin, as well as other cytokines, are further inflammation markers that may be elevated in AD and, importantly, are strongly associated with the development of ACLF.[22,42] These findings promote the hypothesis that the baseline inflammatory profile in AD may a priori discriminate patients with and without courses of ACLF, and only SI capable of inducing end-organ damage is therefore also be thought to be significant for the development of ACLF.[9,23]

In ACLF, the overall inflammatory response is much more pronounced than in SDC, UDC, or pre-ACLF.[42,43] Because a disproportionally high expression of humoral markers is observed but nevertheless bacterial infections occur at a breathtaking rate, it has to be assumed that the cellular immune system is dysfunctional or even paralyzed in ACLF.[27,44,45] Not only in bacterial infection but also in alcoholic ACLF and probably many other precipitators as well, the reason of leukocytosis lies in an increase of neutrophils, which putatively lose their ability to kill bacteria in ACLF.[27,41] Another important antimediator of ACLF is nitric oxide, a potent vasoconstrictor synthesized by the hepatic endothelium. It is capable of counterbalancing vasodilatory stimuli enacted by cytokines but loses its protective function because of ACLF-associated reactive oxygen species generated in the inflammatory portal and sinusoidal milieu.[46]

Metabolic dysfunction

SI in general and AD in particular predispose to hypermetabolic states in which micronutrients, such as glucose, amino acids, and fatty acids, are preferentially held

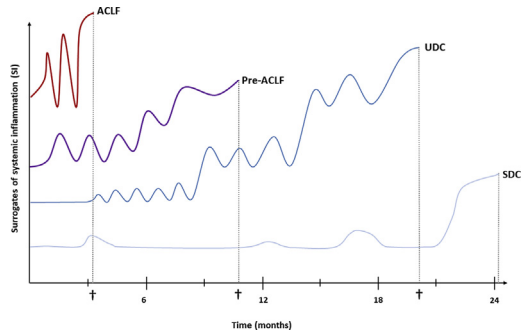

Fig. 1. Schematic visualization of time-dependent systemic inflammation in the four trajectories of acute decompensation.

available for immune cells with high metabolic demand.[47,48] The deprivation of nutrients combined with an inflammatory signature can lead to mitochondrial dysfunction in crucial organs, such as kidney, heart, and liver, thus facilitating the genesis of ACLF.[49,50] Moreover, recent research has shed light on lipid metabolism in ACLF. These lipids are a heterogenous group of inflammatory mediators in blood and tissue, and they are synthesized by the 3 enzymatic families of cyclooxygenases, lipoxygenases, and cytochrome P450 epoxygenases. These enzymes produce a broad array of lipid mediators promoting inflammation and driving neutrophilic bactericidal activity. A panel of these mediators specific for AD has been described, and moreover, leukotriene E4 is capable of differentiating healthy controls from patients with ACLF. On the other hand, LXA_5, which is an anti-inflammatory and proresolution mediator, was significantly underrepresented in ACLF patients.[47]

PRECIPITANTS OF ACUTE DECOMPENSATION

Unidentifiable Precipitants

It is extremely important to identify the precipitant at the pre-ACLF stage. In around 57% of patients with AD, no precipitant is detectable.[9] For many of these patients, it has to be assumed that bacterial translocation and SI cause these events.[28] Bacterial pathogens are translocated from a leaky gut into the blood in a continuous, discontinuous, or burstlike manner and could therefore initiate beginning organ dysfunction.[23,33–36] Indeed, SI is not only observed in UDC and pre-ACLF, but also in patients with compensated cirrhosis or SDC who, importantly, may also have beginning PHT.[20,23,51] It is furthermore noteworthy that SI can apparently be symptomatically treated with intravenous albumin, and survival benefits have been shown in subsets of cirrhotic patients.[52] However, in the other 43% of AD patients, a precipitant is identifiable, and these can therefore be treated more specifically.[9]

Proven Bacterial Infections

Proven infections are defined as bacterial infections with an identifiable source, meaning positive cultures, according to clinical and/or laboratory signs of bacterial infection in patients with cirrhosis, as described before.[53] Gut dysbiosis, loss of intestinal integrity, bacterial translocation, and portosystemic shunting make patients with cirrhosis prone to bacterial infection.[15] Proven infections are the major cause of AD, accounting for 58% of AD patients with an identifiable precipitant.[9] Furthermore, proven infections are equally distributed among SDC, UDC, and pre-ACLF.[11] Importantly, these 3 forms of AD may lead into one another, but they may also cause OFs, which again have a negative impact on the patient's outcome.[24] Routine surrogate markers of SI, such as leukocytes, CRP, and IL-6, are commonly and unspecifically increased in proven infections, making these parameters an insufficient discriminator between infection-triggered AD and infection-triggered ACLF.[23] Severe infections, such as spontaneous peritonitis or pneumonia, are more often found in ACLF, and severe sepsis almost inevitably leads to ACLF, suggesting that the severity of the event itself decides the course for the development and grade of ACLF.[53,54]

About one-half of patients with proven infections develops ACLF, and they develop positive sepsis criteria, most importantly, the SEPSIS-3 criteria and the quick sequential OF assessment, significantly more than patients without ACLF.[17] These patients are characterized by severe SI, most importantly, by elevated levels of leukocytes, CRP, and IL-6.[20,23,54] The 28-day mortality from proven infections in AD patients without ACLF is 5%, but in the case of ACLF amounts to 37%.[17] It is therefore

absolutely mandatory to start antimicrobial treatment as early as possible.[9,55] Thereby, inappropriate antimicrobial therapy is associated with the development of ACLF, and mortality upon inappropriate initial antimicrobial treatment worsens 28-day mortality to 54%, compared with 29% in the case of appropriate treatment.[53] Moreover, broad empiric antimicrobial therapy, including coverage of multidrug-resistant organisms (MDRO), had a higher treatment response and is therefore recommended.[9] However, early deescalation of antimicrobial therapy after isolation of the causative pathogen is strongly recommended in order to minimize the antimicrobial selection pressure and occurrence of MDRO.[56] Therefore, microbiologic cultures should be obtained in every patient with clinically suspected bacterial or fungal infection.[12]

Multidrug-Resistant Infections

The prevalence of MDRO is increasing around the globe, with multidrug-resistant gram-negative bacteria resembling the most threatening class of pathogens.[57] On a general basis, cirrhotic patients with MDRO and extensively drug-resistant organisms (XDRO) are sicker as reflected by MELD (model for end-stage liver disease) and ACLF scores, have more complicated courses, and are admitted to the intensive care unit more often.[58] It is noteworthy that particularly in patients with ACLF, infection with XDRO can be observed more frequently.[17] In patients with cirrhosis, it was shown that severe sepsis and septic shock are associated with the development of ACLF, whereas infection without sepsis was more common in AD patients.[59] Obviously, because these infections are more difficult to treat and empiric therapies fail more often, a higher incidence of ACLF would be expected in the case of infection with MDRO and XDRO.[53,56,59] However, in-depth analyses of ACLF courses in these patients are still lacking. In any case, the finding that XDRO are associated with more severe infections and ACLF deserves further mechanistic investigation.

Severe Alcoholic Hepatitis

Around one-third of AD cases is precipitated by severe alcoholic hepatitis.[11] The clinical course and outcome are similar to patients with proven infections. These patients exhibit a broad array of dysfunctional components within the immune system, which, among others, are intrinsic immunosuppression,[60] a dysfunctional adaptive immune system,[61] dysfunctional neutrophils,[62–64] and oxidative burst mitigating in monocyte function.[65] Moreover, metabolic dysfunction in severe alcoholic hepatitis manifests through changes in mitochondrial function.[66] It was recently shown that the DNA-dependent protein kinase catalytic subunit facilitates the occurrence of alcohol-related liver disease by canonic activation of a pathway with the downstream target p53.[67] Mitochondrial function may therefore serve as a therapeutic target in alcoholic hepatitis.[66] Furthermore, alcohol intake mitigates the intestinal microflora and bile acid metabolism, and, via the gut-brain axis, thus has indirect impact on brain function.[68,69] However, as of now, clinically established treatment of severe alcoholic hepatitis is limited to corticosteroids, which have been shown to improve short-term survival, but not the intermediate or long-term prognosis.

Toxic Encephalopathy

Drug-induced liver injury has long been considered a trigger of AD because of hepatotoxic, nephrotoxic, or neurotoxic effects.[70] However, the PREDICT-2 investigation proved solely neurotoxic drugs administered within the past month to be capable of inducing AD, which were also significantly associated with development ACLF. Neurotoxic drugs precipitating AD were exclusively opioids and benzodiazepines; however,

no significant effect was detected in patients upon administration of hepatotoxic and nephrotoxic drugs.

Gastrointestinal Bleeding with Shock

As was shown in the PREDICT-1 and PREDICT-2 investigations, AD patients who present with gastrointestinal bleeding are significantly more often attributed to "mild" AD stages, that is, SDC and UDC.[9,11] Also, patients with ACLF have a more significant history of bleeding than patients without ACLF.[71] These observations might be explained by the fact that patients with bleeding have significantly less SI than patients with ascites or other decompensation events, and fewer patients with gastrointestinal bleeding without previous decompensation of cirrhosis should therefore develop ACLF, compared with patients with, for example, ascites.[20,71] Of note, bacterial translocation, which is the most important driver of SI, is reliant on the existence of ascites.[28,35]

However, once patients with gastrointestinal bleeding are in circulatory shock, they are at risk of developing AD and ACLF.[9] Furthermore, likelihood of rebleeding doubles in patients with ACLF and history of bleeding, and in that case, these patients are at very high risk of death.[71] However, they do benefit significantly from preemptive or early transjugular intrahepatic portosystemic shunt (pTIPS), compared with ACLF patients who did not receive pTIPS (42-day mortality: 13.6% vs 51.0%; 1-year mortality: 22.7% vs 56.5%; $P = .002$).[71] These observations came in line with previous findings showing that pTIPS could significantly improve survival in severely decompensated patients with variceal hemorrhage and Child C cirrhosis up to 13 points.[72,73] These patients are often on the verge of death, but treatment of PHT with pTIPS has been shown to be a significant relief and is therefore recommended by current international and Baveno guidelines.[12,74,75]

Multiple and Other Precipitants

Some factors, which had been considered putative precipitators in the past, were further elucidated by the second investigation of the PREDICT-2. Among supposed precipitants that were earlier thought to cause AD, drug-induced liver injury is now recognized as a coincidental factor in the pathogenesis of AD.[9] The PREDICT-2 study also significantly contributed to the notion that therapeutic paracenteses, TIPS implantation, and major surgical procedures are not significantly associated with development of AD or ACLF. Importantly, reactivation of viral hepatitis B leads among triggers in many Asian countries, but is only of minor importance in the western world.[26] However, the course of AD becomes much more severe in the case of multiple precipitants, and the inflammatory signature is also drastically enhanced.[9]

SUMMARY

AD is a condition responsible for many deaths in cirrhosis. AD may have different courses from SDC to ACLF, which is the most deadly syndrome in cirrhosis and is characterized by a 3-month mortality of 51%. In absence of OF, SI and PHT determine the course of disease. Significant research must be performed in order to stratify care and develop treatment strategies for AD patients.

CLINICS CARE POINTS

- The severity of acute decompensation is reflected by the degree of systemic inflammation, while the grade of acute-on-chronic liver failure is defined by the numbers of failing organs.

- Precipitants of acute decompensation and acute-on-chronic liver failure must be identified and treated, if possible.
- Patients with variceal bleeding and acute-on-chronic liver failure do benefit from preemptive TIPS placement.
- In patients with bacterial infection, early and adequate antimicrobial treatment may prevent acute-on-chronic liver failure.
- Patients with ACLF-3 should immediately be admitted to intensive care unit for organ support.

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